Aminophylline: Developing Evidence Based Dosage and Monitoring Strategies for Children

Lewis Cooney
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UNIVERSITY OF LIVERPOOL

Department of Women's and Children's Health
Institute of Translational Medicine

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Supervisors
Dr. Daniel Hawcutt
Dr. Ian Sinha

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Abstract

Background: Intravenous aminophylline is used to treat childhood asthma exacerbations. Children who receive aminophylline have serum drug levels measured, due to its purported narrow therapeutic range and variable clearance rates. The results of therapeutic drug monitoring are used to inform subsequent clinical decisions such as dosage. It is not known whether these practices maximise the safety and efficacy profile of aminophylline, and the mechanisms underlying the interindividual variation in clearance rates are poorly understood.

Aims: To assess the evidence base of current aminophylline prescribing practices, and to investigate the mechanisms underlying the variability aminophylline clearance rates.

Methods: Two systematic reviews were undertaken to investigate aminophylline prescribing practices. The first review compared outcomes of children who achieved serum theophylline concentrations between 10-20mg/l with those who did not, and the second review compared different dosage regimens of intravenous aminophylline. An audit of adherence to aminophylline prescribing practices was performed, with subsequent pharmacokinetic analysis. Finally, a pilot cohort study was used to investigate the role of genetics in the variability of aminophylline clearance.

Results: The systematic reviews found a poor correlation between serum drug levels, dosage and clinical outcomes in children receiving intravenous aminophylline. Good adherence to prescribing practices was found in our

audit, however the effectiveness of treatment for acute asthma is no worse if the therapeutic range is not achieved in the first 12 hours of treatment. The cohort study has not yet recruited sufficient participants to assess the effect of genes on aminophylline clearance.

Conclusion: Current dosage and monitoring practices of intravenous aminophylline in childhood asthma exacerbations have a poor evidence base. Measuring aminophylline following administration may be unnecessary, due to the poor relationship between serum drug levels and clinical outcomes, and current dosing strategies may not maximise the benefit of the drug. Most children who receive loading doses do not achieve therapeutic levels, and the mechanisms underlying this variability remain poorly understood.

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List of Abbreviations

A_2	Adenosine receptor A_2
ASS	Asthma severity score
cAMP	Cyclic adenosine monophosphate
CAS/PI	Clinical asthma severity score/pulmonary index
cGMP	Cyclic guanine monophosphate
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
GWAS	Genome wide association studies
FEV_1	Forced expiratory volume in one second
IL	Interleukin
PBPK	Physiologically based pharmacokinetic modeling
PCR	Polymerase chain reaction
PDE	Phosphodiesterase
PK	Pharmacokinetic
PRAM	Paediatric respiratory assessment measure
RCT	Randomized controlled trial
RDS	Respiratory distress score
SD	Standard deviation
SNP	Single nucleotide polymorphism
TDM	Therapeutic drug monitoring

Chapter 1: Introduction

1.1 Background

Asthma is an incurable disease with serious consequences for children and their families. Each year there are 25,000 paediatric asthma admissions to hospital in England, resulting in significant impairment, reduced quality of life for patients and a wider impact on society [1]. The prevalence of asthma is rising [2], with global asthma mortality projected to increase well into the 21st century [3].

All children with asthma are at risk from developing severe exacerbations [4], which have detrimental effects on the wellbeing of children. Exacerbations of asthma are highly distressing, requiring hospital admission and treatment with potentially harmful medicines. Regular exacerbations may result in structural alterations of the airways leading to progressive decreases in lung function and permanent damage to the respiratory tract [5-8]. Frequent asthma exacerbations can have a long-term impact on a child's education due to school absence [9]. The National Health Service spends in excess of £1 Billion on asthma each year, with further economic costs incurred by loss of parental earnings from days off work [10].

Intravenous aminophylline is one of several medicines used to treat acute exacerbations of asthma. Despite being one of the oldest antiasthmatic drugs

still in use, little attention has been paid to its optimum dosage and monitoring strategies in children, meaning patients may not receive the full benefit of the drug. Individuals respond to aminophylline differently, with large variations in clearance rates and clinical efficacy in children [11]**.** The mechanisms underlying interindividual variation in adults and children are poorly understood. This results in an unpredictable clinical response to aminophylline, which may result in therapeutic failure in some patients and toxicity in others. This lack of knowledge means it is difficult to make informed decisions about aminophylline therapy.

This work aims to review the evidence base for the current dosing and monitoring strategies of intravenous aminophylline. This is a vital step in improving asthma outcomes in children. This chapter reviews the current understanding of asthma pathophysiology and the management of exacerbations in children. The pharmacokinetics and pharmacodynamics of aminophylline will be outlined and the evidence surrounding its use will be explored. This chapter further describes the rationale for aminophylline use in children and outlines the potential of this work to improve asthma outcomes.

1.2 Pathophysiology of Asthma

1.2.1 Asthma Triggers

Asthma is a heterogeneous disorder, characterised by chronic inflammation of the lower airways resulting in intermittent and reversible airways obstruction

[12]. Patients with asthma have a heightened responsiveness to stimuli that trigger little or no change in normal individuals. An exacerbation of asthma is a deterioration in symptom control that is sufficient to cause distress or risk to health [13]. Once an exacerbation has been initiated, inflammation and enhanced bronchial responsiveness result in airways obstruction. The clinical manifestations of an exacerbation include shortness of breath, wheezing, coughing and chest tightness.

The precise pathophysiological processes underlying asthma are poorly understood and involve an array of cells, inflammatory mediators and nervous impulses. The composition of these mediators may vary between individuals and different types of asthma [14], resulting in a spectrum of severities, clinical features and responsiveness to treatment.

Atopy is a genetically determined state of hypersensitivity towards environmental allergens, which predisposes individuals to asthma, eczema and allergic rhinitis. Atopy cannot provide a comprehensive explanation to all the clinical features of asthma, as it is not a unified disorder. However it is widely accepted that a dysregulated immune system plays a significant role in asthma pathogenesis.

Atopic asthma exacerbations are initiated following contact between an antigen presenting cell, which uptakes and processes allergens, and a Type 2 T helper cell (TH2). A Th2 weighted immune response is associated with the

promotion of IgE, eosinophils and mast cells [15]. The release of mediators from inflammatory cells provoke an immediate reaction that occurs within seconds, and a late response that starts four to eight hours initial contact with the antigen

The immediate response follows the exposure of an IgE coated mast cell to an inhaled allergen. Chemical mediators such as leukotrienes, histamine, prostaglandins and platelet aggravating factors, as well as stimulation of sub-epithelial vagal receptors, provoke reflex bronchoconstriction. These mechanisms contribute to narrowing of the airways, oedema and mucus secretion that result in immediate asthmatic symptoms [16,17].

Mast cells release cytokines, which recruit eosinophils, leukocytes and neutrophils. These cells amplify and sustain the inflammatory response without exposure to the triggering antigen. Further pro-inflammatory mediators are released including major basic protein, eosinophil cationic protein, eosinophil peroxidase and leukotrienes. These mediators further contribute to airways obstruction and cause tissue damage and inflammation [18].

The distinction between atopic asthma (triggered by allergens) and non-atopic asthma (triggered by non immune stimuli) is helpful from the perspective of pathophysiology, however a significant overlap between the two phenotypes is seen in clinical practice [19,20]. Most childhood

exacerbations are triggered by viruses rather than allergens , and the precise inflammatory pathways in non-atopic asthma are not known, and may involve a defective response to respiratory viruses or sensitization to environmental irritants.

The profile of potential triggers is vast and varies widely between individuals. Several pro-inflammatory pathways may interact contributing to the wide spectrum of clinical and pathological outcomes [21,22]. Asthma can be classified based on its triggers, though this system is not universally accepted (Table 1).

Table 1. Triggers associated with asthma exacerbations and their effects. [20,23,24]

Trigger	**Examples**	**Effect**	**Mechanism**
Viruses	Rhinovirus, Respiratory syncytial virus, human metapneumovirus, influenza virus	Enhanced lower airway damage	Deficient interferon-beta response
Bacteria	Mycoplasma pneumoniae, Chlamydia pneumoniae	Unknown	Unknown
Allergen	Pollen (tree, weed and grass), Fungi, Indoor allergens, animal dander	Enhanced eosinophil response	Allergic sensitization
Occupational	Chemical exposure	Unknown	Unknown
Irritants	Airway pollutants, cigarette smoke	Increased eosinophilic and/or neutrophilic bronchitis	Sensitisation
Psychological	Severe life event, chronic stress	Unknown	Unknown
Medicines	Aspirin, beta blockers	Severe bronchospasm	Unknown
Other	Pregnancy	Unknown	Unknown

1.2.2 Pathobiology

Regardless of the underlying triggers, the final common pathway of asthma is multicellular inflammation, enhanced bronchial responsiveness and airway obstruction [24]. This results a ventilation perfusion mismatch and impaired gas exchange. In severe asthma exacerbations, profound airways obstruction means that arterial oxygen and/or carbon dioxide cannot be maintained at levels required to meet the metabolic demands of the body [25]. Hypersecretion from submucosal glands can result in complete occlusion of the airway lumen by mucous plugs [26]. Acidosis may be caused by a failure to expel carbon dioxide (respiratory acidosis) or ventilatory muscle fatigue (metabolic acidosis). Haemodynamic alterations due to intrapulmonary shunting, increased right ventricular afterload and negative intrapleural pressure may further worsen the ventilation/perfusion mismatch. Asthma exacerbations can be fatal due to exhaustion from the overwhelming work of breathing, combined with hypoxia and its complications leading to respiratory arrest [27].

1.3 Management of Asthma Exacerbations

1.3.1 General Principles

Effective management of a childhood asthma exacerbation involves resolving symptoms, reversing airways obstruction, reducing inflammation and correcting physiological abnormalities [28,29]. Medicines can be used to relax

bronchial smooth muscle and reduce inflammation. This reverses airways obstruction and allows effective gas exchange.

1.3.2 First line treatment

The management of an acute exacerbation of asthma can be divided into first and second line treatments [30]. First line therapy comprises oxygen to correct hypoxaemia [31], and inhaled/nebulised β_2 agonists or ipratropium bromide to provide bronchodilaton [32]. Inhaled medicines selectively treat the pulmonary system resulting in fewer systemic effects. Additional oral or intravenous steroids may be required for their anti-inflammatory effects [33]. There is good evidence to support first line asthma management, and a majority of children require no further treatment.

There is a small subset of children with severe asthma who do not respond to first line therapy and require further treatment for an exacerbation. Drug delivery to the peripheral airways may be impeded by bronchospasm, mural inflammation and mucus impaction [34]. Patients in acute respiratory distress may not be able to generate the necessary flow rates for drug delivery due to fatigue of the respiratory muscles. These factors limit the efficacy of first line treatment, as inhaled medicines are unable to reach their site of action and provide therapeutic benefit.

Intravenous medicines provide an alternative route of drug delivery for children suffering a severe exacerbation of asthma. Intravenous therapies

may be more effective at reversing asthma symptoms, but have the potential to cause serious adverse effects [35]. The decision to commence intravenous treatment must balance the need to prescribe an effective medicine, with the potential harms from adverse effects.

1.3.3 Second Line Treatment

Second line treatment of asthma exacerbations comprises three medicines: β_2 agonists (salbutamol), methylxanthines (aminophylline) and magnesium sulphate. There is a scarcity of relevant studies investigating the beneficial and harmful effects of intravenous therapy in children, and systematic review evidence does not demonstrate superior efficacy of one drug over another [36-39]. This lack of evidence is reflected in conflicting national and international guidelines [30,40-42]. Thus, intravenous treatment regimens vary throughout the United Kingdom and Ireland, and the choice of which drug to use depends on local guidelines, habit and clinician experience, rather than high quality evidence [43] (Table 2).

Table 2. Recommendations for the dosing of intravenous drugs used in the second line treatment of children suffering an exacerbation of asthma

Intravenous therapy	**British Thoracic Society Guideline Recommendations 2014 [44] (level of evidence)**	**Doses used in the UK and Ireland [43]**
Salbutamol	Consider early addition of a single bolus dose of intravenous salbutamol (15 μg/kg over 10 min) in a severe asthma attack where the patient has not responded to initial inhaled therapy (1^+)	Bolus/load: 2–15 mg/kg over 5–40 min Infusion: 0.3–5 mg/kg/ min
Aminophylline	Consider aminophylline for children with severe or life-threatening asthma unresponsive to maximal doses of bronchodilators and steroids (2^+)	Bolus load: 10 mg/kg– 200 mg (total) over 30 min Infusion: 0.5–1.0 mg/kg/ h
Magnesium sulphate	Magnesium sulphate is a safe treatment for acute asthma although its place in management is not yet fully established. (1^+)	Bolus: 5–54 mg/kg over 20–30 min Infusion: N/A

1^+ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias, 2^+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

The optimum use of intravenous therapy in childhood exacerbations of asthma requires more than simply the selection of the right drug. The dosage and monitoring strategies have important influences on the risk/benefit profile of many drugs, which influences an individual's therapeutic response. Ethical and practical challenges in undertaking pharmacokinetic studies in paediatrics

mean many children are denied the benefit of optimum asthma treatment, or are harmed from unpredicted adverse effects [45]. As the ideal prescribing practices of intravenous therapies in childhood asthma are not known, various dosing and monitoring strategies are used in studies comparing treatments. This lack of clarity means available literature may mislead clinicians wishing to make evidence based decisions regarding asthma treatment. Only when the optimum prescribing practices of intravenous antiasthmatic drugs are known, can definitive randomised controlled trials be undertaken comparing different asthma drugs [43].

1.4 Intravenous Aminophylline in Childhood Asthma Exacerbations

1.4.1 Aminophylline in acute asthma

Aminophylline is a mixture of theophylline and ethyldiamine. Theophylline is the active compound with anti-asthmatic properties, whilst ethyldiamine is an excipient, which confers greater solubility in water.

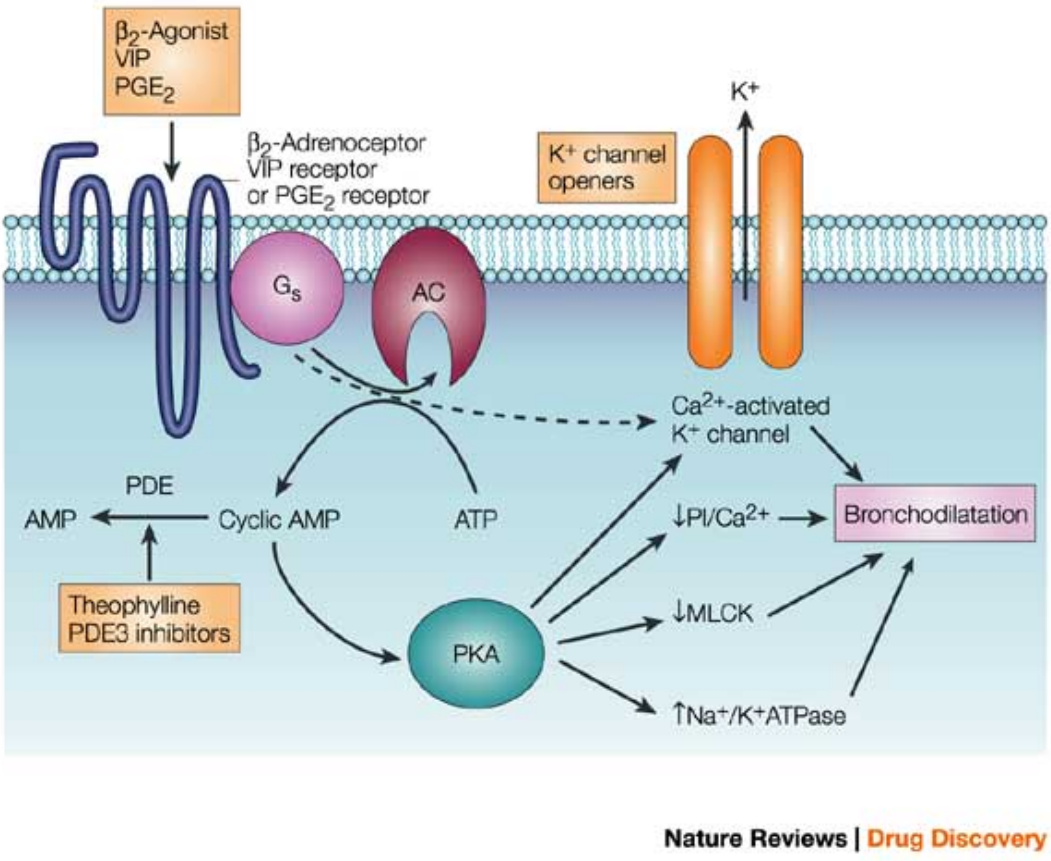
The use of aminophylline in asthma increased during the 1970's and 1980's due to a better understanding of its pharmacokinetics and pharmacodynamics, improvements in serum measurement and the development of slow release preparations [46]. In the 21st century, the use of aminophylline in asthma exacerbations has largely been surpassed by inhaled medicines and systemic steroids. Aminophylline has a significant side effect

profile and is a relatively weak bronchodilator meaning it is only reserved for more severe exacerbations. An appreciation of the precise pharmacokinetic and pharmacodynamic properties of aminophylline is important in improving its prescribing practices.

1.4.2 Mechanism of action

Several mechanisms have been proposed for aminophylline, however its precise antiasthmatic mode of action is unknown. Bronchodilation, mediated by inhibition of phosphodiesterase (PDE) enzymes, is the most commonly accepted mechanism for the clinical efficacy of aminophylline. Phosphodiesterase enzymes degrade the phosphodiester bond within the second messenger molecules, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Inhibition of PDE causes an increase in the concentration of cAMP and cGMP within smooth muscle cells resulting in a reduction in cellular calcium concentrations, and activates protein kinase A. This increases the activity of myosin light-chain kinase and decreases the activity of myosin light chain phosphatase. Decreased intracellular calcium concentration and myosin light chain kinase activity leads to bronchial smooth muscle relaxation and reversal of airways obstruction (Fig 1). Inhibition of PDE also accounts for the many side effects of aminophylline including headache, nausea, vomiting and increased acid secretion.

Fig 1. Molecular mechanisms of action of bronchodilators. [47]



VIP Vasoactive intestinal peptide, PGE_2 Prostaglandin E_2, AC adenylyl cyclase, G_s stimulatory G-protein, PKA protein kinase A, K_{Ca} calcium activated potassium channels, PI phosphinostide, MLCK myosin light chain kinase.

Other mechanisms for the anti-asthmatic effect of aminophylline have been proposed. As knowledge of inflammatory pathways develops there is evidence that theophylline has anti-inflammatory and immunomodulatory effects [48]. Theophylline demonstrates adenosine receptor antagonism, which may further explain the beneficial and harmful effects of aminophylline [49]. Blockade of A_2 receptors may prevent histamine release from mast cells and inhibit bronchoconstriction, whilst A_1 antagonism is likely to account for its serious side effects such as seizures and cardiac arrhythmias. Other purported anti-inflammatory effects include raising the levels of interleukin-10 [50]

reducing the expression of inflammatory genes, and reversal of steroid resistance through activation of histone deacylases [51] (Box 1).

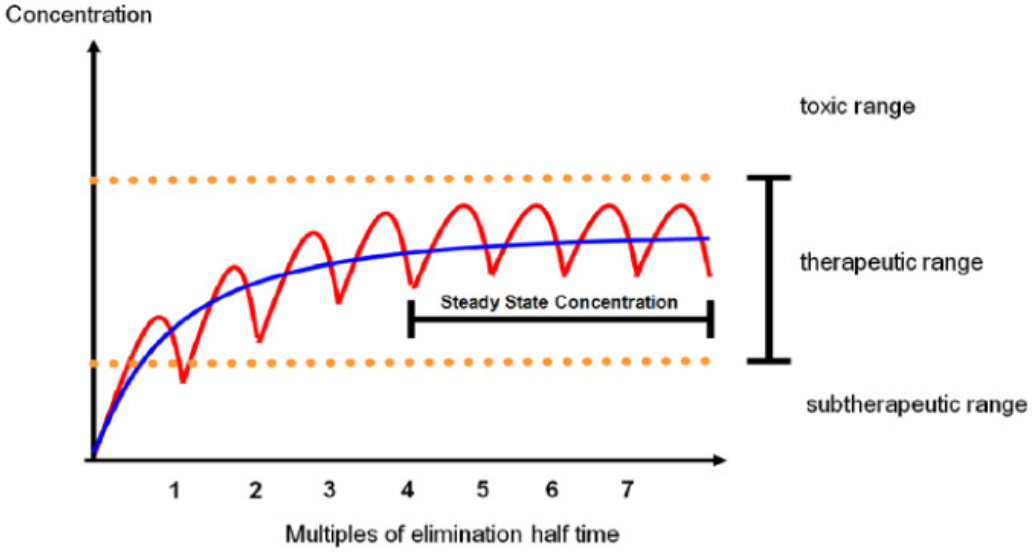
Box 1. Proposed mechanisms of action of theophylline**.** [52]

Phosphodiesterase inhibition Adenosine receptor antagonism Inhibition of nuclear factor κ BIncreasing Histone deacetylase 2 via Inhibition of phosphoinositide 3-kinase- δ Increasing IL-10 secretion Increasing Apoptosis of inflammatory cells (neutrophils, T cells)

1.4.3 Pharmacokinetics

The steady state concentration of aminophylline is when the overall intake of a drug is in a dynamic equilibrium with its elimination [53]. Once steady state has been achieved, serum levels of theophylline remain relatively constant and its therapeutic properties can be maximised (Fig 3). Aminophylline has a long half-life meaning it is eliminated from the body relatively slowly [54-56]. Serial administration of aminophylline could result in delayed therapeutic efficacy as it takes around five half lives to achieve steady state concentrations. In an acute exacerbation of asthma, it is important that the therapeutic effects of aminophylline occur rapidly to hasten recovery. However, dosing children too quickly may result in overdose, with the resulting toxic concentrations taking a long time to clear.

Fig 2. State concentration following serial admission of a medicine [57]



The rationale for current prescribing practices of intravenous aminophylline is based on a purported correlation between drug concentrations in the blood and clinical efficacy [58]. Based on this assumption, there is a theoretical window of serum theophylline concentrations that provides optimum anti asthmatic action with minimal adverse effects. This therapeutic range of aminophylline is said to be narrow, meaning small differences in blood concentrations may lead to either therapeutic failure or increased likelihood of adverse drug reactions. Current guidelines recommend aiming for serum concentrations between 10-20mg/l [30,44].

The plasma theophylline concentration resulting from a given dosage is relatively uncertain due to the high level of interindividual variation in theophylline clearance rates. As the correlation between dosage and serum concentration is poor, theophylline measurements in the blood are used as surrogate indicators of efficacy [59].

1.4.4 Therapeutic drug monitoring

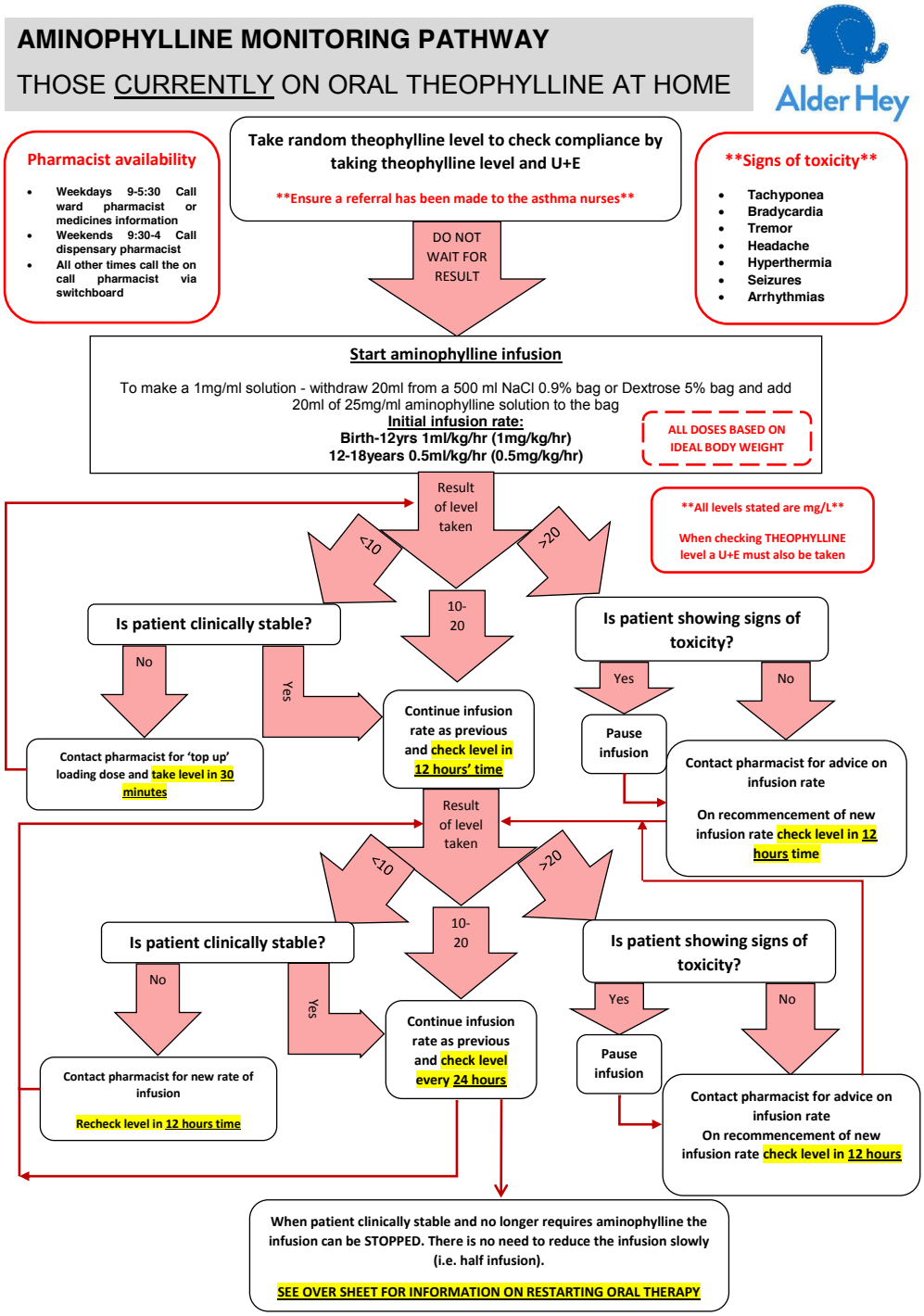
Aminophylline is subject to therapeutic drug monitoring (TDM) due to its narrow therapeutic range, significant adverse effect profile and unpredictable pharmacokinetics. Patients who treated with aminophylline receive blood tests, which are used to measure serum drug levels in a laboratory. These results are compared to a reference range, and subsequent dosages are adjusted allowing individualization of aminophylline dosage that reflects the child's pharmacokinetics.

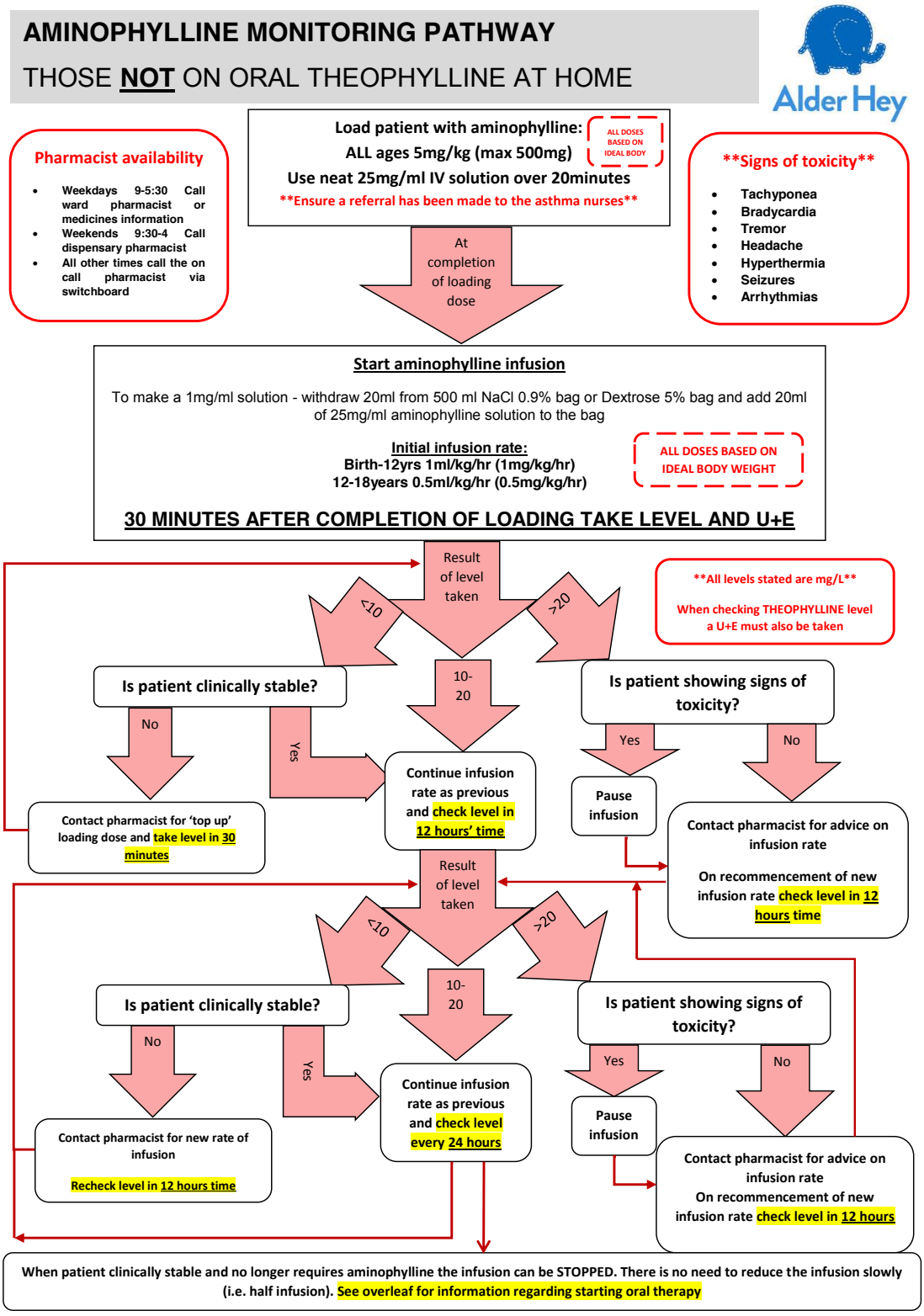
Guidelines for prescribing aminophylline in children are complex. There are two separate algorithms based on whether a child takes a regular oral theophylline medication. Patients who do not take regular oral theophyllines receive a 5mg/kg loading dose and an infusion at a rate of 0.5mg/kg/hr to 1.0mg/kg/hr depending on the age of the child. Oral preparations of theophylline such as Nuelin SA and Slo-Phyllin are prescribed for chronic asthma. When these children present to emergency departments requiring intravenous aminophylline, their serum theophylline concentrations are not known and a uniform loading dose in these patients may result in toxicity. These patients receive an aminophylline infusion on admission. Once their serum levels are confirmed, a decision is made on whether a top up loading dose is required.

Once treatment with intravenous aminophylline has been initiated, TDM is

used to guide further dosage. Serum levels should be checked every 24 hours, with infusion rates adjusted so that children maintain serum theophylline concentrations between 10-20mg/l (Fig 3).

Fig 3. Alder Hey guidelines for aminophylline dosage and monitoring





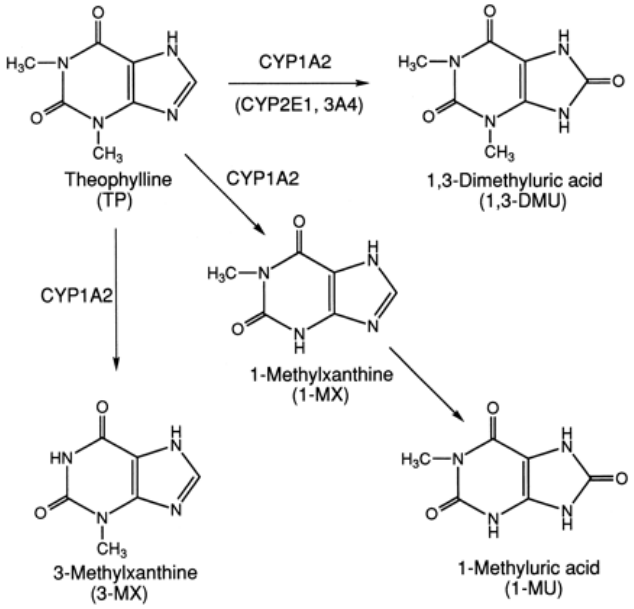
Monitoring blood theophylline levels in patients receiving aminophylline represents an early effort to tailor aminophylline dosage to an individual's

pharmacokinetics. Infusion rates are altered to keep serum theophylline concentrations within its therapeutic range. The assumption that a serum theophylline concentration between 10-20mg/l represents the maximum efficacy and safety of aminophylline is based on improvements in spirometry measurements in adults who are not acutely unwell [60-62]. Adults are inappropriate study participants on which to base paediatric treatment, and one wouldn't measure spirometry in acute exacerbations to establish a serum theophylline concentration that represents the maximum efficacy and safety of the drug.

1.4.5 Cytochrome P450 Enzymes

The cytochromes P450 (CYPs) are a superfamily of haeme containing enzymes responsible for the demethylation of theophylline to 1-methylxanthine and 3-methylxanthine. The removal of the methyl group from theophylline renders it pharmacologically inactive. At theophylline concentrations used in clinical practice, CYP1A2 is the enzyme responsible for drug metabolism. At very high theophylline concentrations, the CYP2E1 enzyme has an additional role in demethylation (Fig 4).

Fig 4. Metabolic pathways of theophylline in humans [63]



The activity of CYPs is influenced by a unique combination of genetic and environmental factors that alter its expression. Factors that increase the expression of CYP1A2 are known as inducers, and include smoking, caffeine and rifampicin**.** Under these circumstances, clearance rates of theophylline are increased, resulting in lower serum concentrations and potential therapeutic failure. Conversely, inhibitors of CYP1A2 such as the oral contraceptive pill, quinolones and isoniazid, may decrease theophylline clearance leading to toxicity [64]. Genetic factors such as the influence of polymorphisms of the gene that codes for the *CYP1A2* enzyme may further influence aminophylline disposition.

The optimum dose of aminophylline may be specific to an individual's pharmacokinetics, and individualization aminophylline therapy could maximise

the efficacy and safety of the drug. As the factors underlying interindividual variation are not known, initial dosage of aminophylline is low to circumvent side effects, with subsequent doses titrated to the individual demands of patients. This process is slow and may not represent the best use of intravenous aminophylline. These factors mean patient response to aminophylline is highly variable, and there may be scope to target therapies to specific groups of patients based on prior knowledge of their clinical and genetic profiles.

To improve asthma outcomes in children, it is important to determine whether patients experience important benefits from a particular dose or monitoring strategy of aminophylline [65]. The selection of appropriate outcomes is crucial when assessing drug dosage and monitoring. Since the establishment of the therapeutic range in the 1960's and 1970's, there has been a greater understanding of the importance of measuring clinically relevant outcomes when assessing the efficacy of an intervention in acute asthma. A set of core outcomes has been developed in conjunction with patients, families and healthcare professionals, in an effort to improve the clinical relevance of studies [66]. However, there is no specific outcome set for acute asthma. An investigation into whether serum levels between 10-20mg/l correlate with a true improvement of children suffering an acute exacerbation of asthma is required. This will be the first step in stratifying aminophylline therapy.

1.4.6 Interindividual variation

Asthma is a common condition, affecting a diverse population encompassing many ages, ethnicities and severities. Increasing awareness of the heterogeneity of asthma may help to explain the variability in response to treatment [67,68]. The identification of responders and non-responders for a given medicine may be a key step in maximising the efficacy and safety of current asthma therapies. The sources of variability in aminophylline response are multifactorial and may be determined by genetic, environmental and host factors (Box 2).

Box 2. Factors that may influence treatment response to aminophylline

Genetics
Age
Developmental status
Severity of baseline inflammation
Remodelling from chronic disease
Sensitivity towards environmental triggers
Exposure to environmental triggers
Interactions with other drugs
Adherence to asthma therapy
Drug allergies

Personalised medicine involves tailoring treatment to meet the needs of individual patients based on their predicted response to a drug [69]. Personalised medicine relies on an understanding of the precise mechanisms which determine responsiveness to treatment. This requires the consideration of many factors that may influence how patients respond to medicines, from the genetic, molecular and cellular to the environmental. The goal of

personalised asthma therapy is steering selected patients to the right drug, at the right dose at the right time to maximise the risk benefit ratio of interventions.

1.4.7 Age specific doses

Age is a well-recognized factor in determining the optimum treatment for acute asthma. The established management for adults suffering an acute exacerbation may be inappropriate in children, and separate medicines and doses may need to be recommended [30]. Ethical and practical limitations of conducting drug research in children means the specific pharmacokinetics and pharmacodynamics of many drugs are poorly understood in paediatrics. Age and weight specific doses are already recommended when aminophylline is used in acute asthma. Children under 11 receive higher relative doses per unit of body weight to account for their observed faster clearance rates [11].

1.4.8 Pharmacogenomics and Pharmacogenetics

Pharmacogenomics is the study of all the genes in the genome that may determine drug response at a cellular, individual or population level response [70]. In asthma, this encompasses the study of asthma genes associated with susceptibility, and genes encoding for drug metabolism enzymes, transporters, receptors and transduction pathways. Pharmacogenetics is a more specific term, usually referring to the study of specific variations in DNA sequence in relation to drug [67]. Pharmacogenomics and pharmacogenetics

may be important tools in stratifying asthma therapy. It is hoped that combining genetic information with pharmacotherapeutic data will enable the development of tailored regimens that maximize efficacy and minimize adverse events in treating acute exacerbations of asthma.

The number of potential determinants of response to therapy is vast. If tailored asthma therapy is to become a reality, it requires a holistic investigation into the determinants of interindividual variability of a specific drug. If such an association between a genetic/environmental factor and treatment response is found, there is potential to stratify intravenous aminophylline for children suffering an acute exacerbation of asthma.

1.5 Aims and Objectives

This work aims to improve the evidence base for aminophylline dosage and monitoring for children suffering an acute exacerbation of asthma.

Chapter two is aims to systematically review current evidence for the optimum therapeutic range of intravenous aminophylline in children. This is the first systematic review investigating the optimum therapeutic range of a drug and this chapter explores the methodological challenges of conducting studies of this type.

Chapter three is another systematic review, which aims to investigate the evidence base of the current dosing recommendations of aminophylline (5mg/kg bolus followed by an infusion between 0.5-1.0mg/kg/hr).

Chapter four aims to assess adherence aminophylline prescribing guidelines, and describe the pharmacokinetics of aminophylline in children suffering an acute exacerbation of asthma. This is an audit of current prescribing practices of at Alder Hey children's hospital, and compares the outcomes of children who achieve 'therapeutic' vs 'non therapeutic' serum levels.

Chapter five describes the development of a pilot study investigating the pharmacogenetics of aminophylline. This prospective cohort study aims to investigate the role of *CYP1A2* polymorphisms of aminophylline disposition, and clinical outcomes of children.

Chapter six discusses the findings from these works and their relevance for clinical practice.

Chapter 2: The Evidence for Achieving Intravenous Theophylline Levels between 10-20mg/L in Children Suffering an Acute Exacerbation of Asthma: A Systematic Review

2.1 Background

2.1.1 Therapeutic drug monitoring evidence

Therapeutic drug monitoring (TDM) is predicated on a definable relationship between clinical outcomes and serum drug concentrations [58]. To maximise the efficacy and safety of intravenous aminophylline, TDM practices should be based on evidence of clinical improvement. Target theophylline concentrations between 10-20mg/l are the most widely accepted [30,44], however the evidence for this recommendation is unclear.

The therapeutic range of intravenous aminophylline is based on improvements in spirometry in adults. Although the relationship between serum levels above 10mg/l and improving FEV_1 and is consistent across studies [61,62,71,72], this is a poor evidence base on which to guide therapy for children in the acute setting (Chapter 1). A small number of studies report

an increase in adverse effects above 20mg/l [73-75]. An investigation into the relationship between serum theophylline concentrations and clinical improvement of asthma exacerbations is required to improve prescribing practices.

Systematic reviews condense large amounts of heterogeneous information into a manageable format that can inform clinical decisions. They are a key component of the evidence based medicine movement and provide the best possible estimate of any true effect.

2.1.2 Aim

This chapter aims to review the evidence for the current therapeutic range of intravenous aminophylline (10-20mg/l). It outlines the basic principles of systematic reviews, and explores the methodological considerations when undertaking a review of this type.

2.2 Methods

2.2.1 Study design

A systematic review of studies investigating the use of intravenous theophyllines in acute asthma in children that report both relevant clinical outcomes and theophylline levels.

2.2.2 Included Studies

Included studies were parallel and crossover randomized controlled trials

(RCTs) comparing two or more therapeutic ranges for intravenous theophyllines in children and adolescents (aged 19 or younger) with acute asthma. RCTs comparing intravenous theophyllines with placebo were also included, if a measure of serum theophylline levels was reported for the two treatment groups, retrospective or prospective observational studies were also eligible if they reported results for both clinical outcomes and therapeutic levels measured.

Studies including adults (20 years and older) and children were excluded, unless the paediatric data were reported separately. Children have differing pharmacokinetic and pharmacodynamic properties when compared with adults [76-78]. These differences will affect the safety and efficacy profile of intravenous aminophylline, and therefore its optimum therapeutic range in asthma. Studies utilizing aminophylline for an indication other than asthma were excluded (e.g. neonatal apnoea and tuberculosis), as measures of drug efficacy are dependent on its indication. As acute versus chronic indications have different risk benefit rations, this study focused on acute exacerbations only.

2.2.3 Outcomes

If the results of the systematic review are to identify appropriate therapeutic ranges, selected outcomes must reflect beneficial and harmful effects of the drug, which are relevant to clinical practice in context of the population of

interest. Outcomes must be selected prior to literature searching to prevent over reliance on inappropriate outcomes that may not be relevant [79].

Although spirometry provides an objective measurement, it is an imperfect marker of asthma improvement. Spirometry is effort dependent frequently inaccurate in the very young or ill, and correlates poorly with asthma symptoms [80-82]. Since therapeutic ranges were established in the 1960's, the importance of selection outcomes that reflect clinical improvement of asthma exacerbations has been recognized [65,66,83]. This systematic review uses a core outcome set that has been developed in collaboration with clinicians, patients and their families to ensure that the measured outcomes translate into real world improvement [66].

The pre-specified primary outcomes were i) time until resolution of symptoms ii) need for mechanical ventilation, and iii) mortality. Secondary outcomes were i) days until discharge criteria are met ii) actual discharge from hospital and iii) adverse effects as defined and reported by authors. Forced expiratory volume in one second was used to assess the incidental relationship between serum concentrations and spirometry. Studies must have reported at least one outcome to meet our inclusion criteria.

2.2.4 Identification of studies

Few primary studies directly investigate therapeutic ranges [84,85] and a range of scenarios were anticipated prior to searching. Several levels of study

design were considered, which the available evidence to be systematically graded. This avoided placing inappropriate weight on studies that are methodologically less robust when formulating conclusions.

The optimal scenario was a systematic review of RCTs comparing two or more therapeutic ranges of intravenous aminophylline. RCTs were considered the highest grade of evidence as randomization minimises selection bias, and accounts for unknown confounding variables.

The suboptimal scenario incorporated either observational data or indirect comparisons between clinical trials such as RCTs comparing aminophylline to placebo/other treatment. Observational data may be obtained from cohort studies, case-control studies, or case series. Indirect evidence may be gained from identifying RCTs that have compared the drug against a common comparator (likely placebo), and then analysing whether studies, in which a higher serum concentration was achieved, demonstrated superior outcomes.

Electronic search engines were used, which include several databases to identify studies for this review. Included databases included: medline (complete), Excerpta Medical database (EMBASE), PubMed Central, Compendex, World Textile Index, Fluidex, Geobase, Biobase, CINAHL and PSYCHinfo. Unpublished data was identified by searching the Cochrane Register of Controlled Trials (CENTRAL) to avoid the problems of publication

bias. CENTRAL provides additional evidence that may not be included in other databases [86].

The following terms were used in the literature search in September 2015 with no date or language restrictions:

((aminophylline OR xanthine OR phyllocontin OR theophylline OR pde4 inhibitor OR phosphodiesterase 4 inhibitor OR caffeine) and (intravenous OR IV OR parenteral) AND (acute asthma OR asthmaticus OR severe asthma OR "hospital*ed" OR asthma attack") AND (child* OR adolescen* OR infan* OR p*ediatric))

Brand names of aminophylline were included, as well as the class of drugs to which it belongs (pde4 inhibitor). As acute exacerbations are frequently described using variable terminology [27], terms were included that could capture studies describing the following phenomenon: acute asthma, asthma exacerbations, status asthmaticus, asthma attacks. Numerous paediatric search terms were used as there is no consensus on the strategy for identifying studies relevant to children [87]. The search term was not included "therapeutic range" as many relevant studies may not include this term in their keywords or abstract and its inclusion would result in an overly specific search strategy, and the potential exclusion of relevant studies.

One reviewer (LC) screened all abstracts and a second reviewer (IS or DH) checked the eligibility of abstracts after initial screening, and full studies included in the review. Reference lists were screened for other eligible studies.

2.2.5 Assessment of Quality and Risk of Bias

An assessment of quality allows the reviewers to present the degree to which the results in the available literature are valid and robust, and whether conclusions that impact on clinical practice should be made. There is no appraisal tool for systematic reviews investigating the optimum therapeutic range of a drug. Our methods for quality assessment must encompass the several scenarios anticipated based on the available evidence. As many different study designs may be included in this review, numerous appraisal tools were considered (Table 3).

Table 3. Tools used for appraisal of quality which may be used in this review

Study Design	**Available Tools**
Systematic Review	Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) - for reporting
Randomized controlled trials	Critical Appraisal Skills Programme (CASP) – Reporting and Conduct
Cohort studies	Critical Appraisal Skills Programme (CASP) – Reporting and Conduct
Case control studies	CASP tool for conduct and reporting
Case reports	CARE tool for reporting

There are specific considerations of quality assessment when undertaking a systematic review of therapeutic ranges, which may not be included in quality assessment tools.

The measurement of drug concentrations in serum provides a snapshot of the dynamic process of drug clearance. The timing of measurement therefore influences the results of therapeutic drug monitoring [88]. Drug levels should be measured at the same time across participants to give an accurate representation of drug levels achieved.

Deciding the upper limit of a therapeutic range requires relevant data on the harmful effects of drugs. Ad hoc measurement of adverse effects carries the risk of selective outcome reporting [89], which could misinform the upper limit of a therapeutic range. These factors were taken into consideration when assessing quality.

The Cochrane risk of bias tool was used to assess aspects of trial design, conduct, analysis and reporting that would cause results to differ from the true values [79]. This tool would be used to assess all included RCTs in this study.

2.2.6 Data extraction and analysis

From each study we identified the theophylline levels achieved in the research participants (and when these were measured) and, if stated, the desired

target range. We extracted data around our selected outcomes, at whichever timepoints they were reported. We also recorded the age range of participants. From RCTs, exclusion criteria, control medication, concomitant medication and statistical significance of results were also noted.

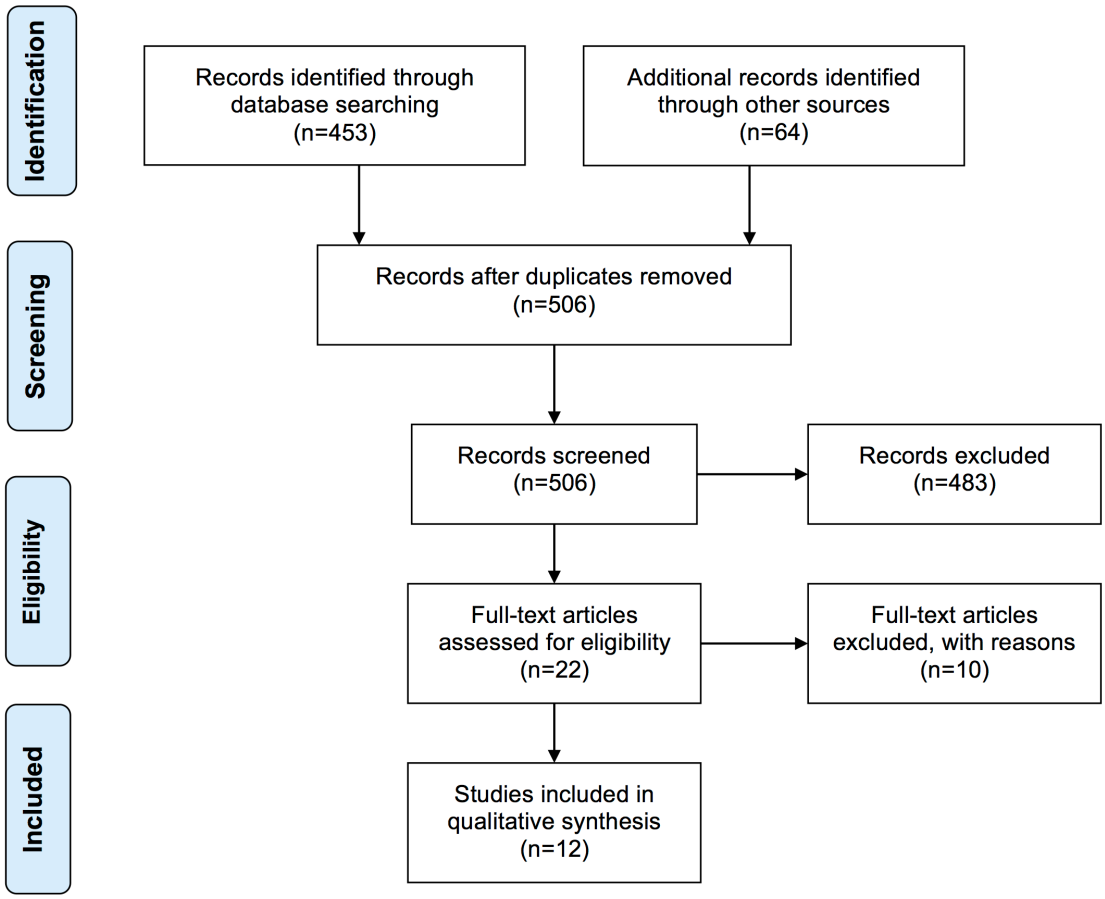
Systematic reviews require the methods of statistical analysis to be devised prior to searching. As the availability of relevant evidence was not known, several scenarios were anticipated. In our optimal scenario, a meta-analysis was planned if numerous studies that investigate the relationship between serum drug concentrations were identified. This would allow a quantitative summary of the relationship between serum drug concentration and clinical efficacy. A descriptive analysis was planned if quantitative data synthesis was not possible.

2.3 Results

2.3.1 Included Studies

A total of 506 studies were found using the search criteria, with 22 full text articles screened for eligibility. We excluded 10 full text articles (appendix) with the remaining 12 articles included in the review (Fig 5).

Fig 5. Search Results of the systematic review investigating the optimum therapeutic range if intravenous aminophylline



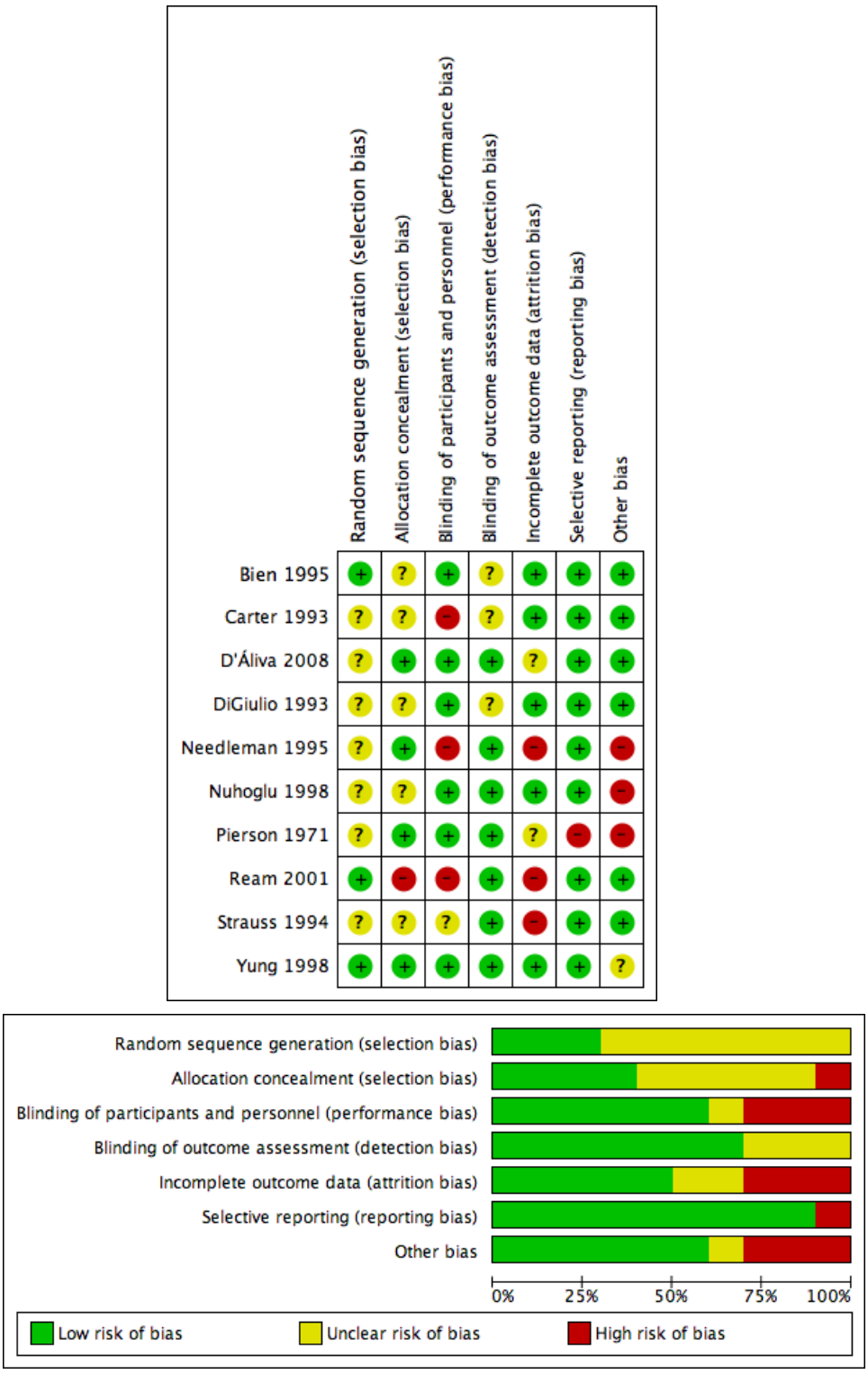
We found no RCTs comparing different therapeutic ranges of aminophylline and we used indirect data for our analysis. We included ten RCTs comparing theophylline with placebo, and two retrospective observational studies. There were insufficient studies comparing aminophylline to a comparator drug (eg salbutamol or magnesium sulphate) for data analysis comparing, hence only RCTs comparing aminophylline to placebo were included.

2.3.2 Quality of included studies

Of the ten randomized controlled trials, two studies gave no data on adverse effects [90,91], two studies reported side effects unsystematically [92,93] and six reported adverse effects thoroughly using prospective methods clearly outlined in the methodology [94-98].

Each study was assessed for its risk of selection bias, performance bias, detection bias, attrition bias and reporting bias. The results of the Cochrane risk of bias assessments are shown in Fig 6. Three studies were classed at high risk of attrition bias, one at high risk of reporting bias with respect to symptom scores, and three at high risk of reporting bias of adverse outcomes. The other domains of bias were classified as low or unclear risk in most studies.

Fig 6. Assessment or Risk of Bias of included studies in a systematic review investigating the optimum therapeutic range of intravenous aminophylline



The CASP assessments conducted on the two observational studies are presented in Table 4.

Table 4 Assessment of quality in observational studies.

	Dalabih 2014	**Fox 1982**
Clearly focused issue	🡻	🡻
Acceptable recruitment	🡻	🡻
Adequate exposure measurement	🡻	🡻
Adequate outcome measurement	🡻	🡻
confounding factors identified	🡹	🡹
Complete follow up?	🡹	🡹
Result precision	**?**	**?**
Believable results	🡻	🡻
Applicable to local population	🡻	🡻
Consistent with other evidence	**?**	🡻

🡻 low quality domain, 🡹 high quality domain, **?** unclear quality domain

2.3.3 Study Characteristics

The theophylline levels reached, primary outcomes and secondary outcomes are shown in Tables 5-7. Studies were ranked from lowest theophylline level achieved to highest, this process was limited due to inconsistent reporting.

Table 5. Characteristics of included RCTs

First author, Location, age range of participants	Timing of theophylline level measurement	Primary Outcome(s)	Other medication used
D'Avila 2008 Brazil, 2-5 years	Not reported	Oxygen and salbutamol requirements, llength of stay	β_2 agonists, steroids
Pierson 1971 USA, 5-17 years	24 post admission	FVC and FEV	Adrenaline
Ream 2001 USA, 13-17 years	30 to 60 mins post loading and 4 to 6 hours after beginning the infusion	Time to reach CAS/PI ≤3	β_2 agonists, ipratropium bromide, steroids, terbutaline
Bien 1995 USA, 2-10 years	30 mins post loading, 6 hours later, once a day at therapeutic steady state level	Time to reach CAS/PI ≤3	β_2 agonists
Strauss 1994 USA, 5-18 years	30 minutes and 4 hours post loading and then approximately every 12 hours.	Length of stay	β_2 agonists, steroids
DiGiulio 1993 USA, 2-18 years	1 hour after starting infusion	Number of hours elapsed before CAS ≤ 2	β_2 agonists, steroids
Nuhoglu 1998 Turkey, 2-16 years	Within one hour of the completion of the loading dose, and 12–18 hours later	Salbutamol requirements, CAS/PI	β_2 agonists, steroids
Carter 1993 USA, 5-18 years	6, 12 to 24, and then every 24 hours thereafter	Percentage of predicted FEV1, CAS/PI	β_2 agonists, steroids
Needleman 1995 USA,2-18 years	30 mins and 60 mins after initial bolus, 4 to 6 hours later on steady state infusion	Length of stay, CAS/PI	β_2 agonists, steroids
Yung 1998 Australia, 1-19 years	12-18 hours post bolus	Length of stay in hospital, FEV1, FVC, oxygen saturation, CAS.PI	β_2 agonists, ipratropium bromide, steroids

Table 6. Results of RCTs

Study, number of participants (intervention vs control)	Theophylline levels achieved	Time until resolution of symptoms	Need for mechanical ventilation	Date until discharge criteria are met	Actual discharge	Adverse effects	Spirometry
D'Avila 2008, 30 vs 30	7.37mgl ±1.39mg/l (mean±SEM)	Not measured	Excluded	Not measured	No significant difference in length of hospital stay 30.8h in aminophylline group vs. 40.0h in placebo (p=0.48)	Not measured	Not measured
Pierson 1971, 11 vs 12	5-15mg/l	Not measured	Not measured	Not measured	Not measured	Not measured	Significantly improved FEV1 and FVC at 24 hours compared with placebo (89% vs 62% p<0.001)(18% vs 68% p<0.001)
Ream 2001, 23 vs 24	11.2±0.4mg/l after loading dose, 12.5±1.2 mg/L at 8 to 12 h average daily level of 14.5 ± 0.7 mg/L.	Those receiving theophylline achieved a CAS of <3 sooner than control subjects (18.6±2.7 h vs 31.1±4.5 h; p<0.05)	All subjects intubated before infusion	Time to discharge criteria in theophylline group 29.8±4.9 hours vs. 36.4±5.5 hours in control p>0.05 In those not receiving mechanical ventilation. In subjects receiving mechanical ventilation 74.8±8.9 in theophylline group vs. 189.3±34.3 p<0.05	Length of stay in critical care in theophylline (3.9±0.3 days) vs. control (8.8±1.5 days) p<0.05, length of stay in hospital 8.3±1.5 days vs. 13.0±1.0 days p<0.06	High rate of adverse effects, no data on how these correlate to serum levels, did not differ between controls	Not measured
Bien 1995, 19 vs 20	10.1mg/l (mean) post bolus, 11.8(mean) at approximately 8 hours	CAS at 24 hours 2.0 in theophylline group 2.6 in placebo group p>0.05	Excluded	Not recorded	Not measured	Statically higher rates of nausea, and vomiting in theophylline group p≤0.05 but not insomnia p=0.08	Peak flow only available in 5 patients, statistical analysis not possible

Study, number of participants (intervention vs control)	Theophylline levels achieved	Time until resolution of symptoms	Need for mechanical ventilation	Date until discharge criteria are met	Actual discharge	Adverse effects	Spirometry
Strauss 1994, 14 vs 17	Mean theophylline level 12.0±2.5mg/l mean of peak 14.3mg/l	Not measured	Excluded	Not measured	Hospital stay in aminophylline group 2.58±1.5 days vs 2.33±1.3 days in placebo group p>0.2	Significantly higher rates of side effects in aminophylline group (43%) in vs control (6%) in p<0.05 2 patients removed due to toxicity, headache and abdominal pain, one patient theophylline level of 23mg/l and experienced nausea and vomiting, all other patients had levels >20mg/l.	PPFR final 0.80±0.22 in aminophylline group vs 0.79±0.22 in placebo p>0.2
DiGiulio 1993, 16 vs 13	13.1±3.4mg/l (mean) throughout study	30.4±16.8 in intervention vs 27.0±10.3 hours in control; p = 0.51	Excluded	30.4±16.8 hours in aminophylline vs. 27.0±10.3 hours in control; p = 0.51. Discharge criteria was equated to CAS≤2	Not measured	Not statistically significant compared with control group	Not measured
Nuhoglu 1998, 18 vs 20	10.5-14.3mg/l throughout study	CAS at 24 hours 2.1 placebo and 2.0 in aminophylline p=0.8452	Not measured	Not measured	Not measured	No significant difference between groups. 2 patients with adverse effects were documented with therapeutic serum theophylline levels. No significant difference from control.	Only 2 children were able to perform spirometry, statistical analysis not possible
Carter 1993 12 vs 7	10-20mg/L in all patients throughout study	Median CAS/PI at 36 hours 2 in intervention and control groups p=1.0	Excluded	Not measured	Not measured	no clinically relevant adverse effects, no data on how these correlate to serum levels, did not differ significantly between controls	No significant difference in FEV1 at any time in the study p>0.05
Needleman 1995, 22 vs 20	10-20mg/L in all patients throughout study	Fall in asthma score in treatment group 3.05±3.25 vs. 2.38±2.19 in placebo p=0.482	Excluded	Not measured	Length of stay in theophylline group 52.3±32.3 hours vs. 48.2±26.6 hours p=0.654	Not measured	Not measured
Yung 1998, 81 vs 82	<10mg/l in 4(5%), 10-14.5 in 26(33%) 14.5-20 in 42(53%) and >20 in seven(9%) post loading dose, three (7%), 15 (35%), 11 (26%), and 13 (31%),	Not measured	All subjects intubated before infusion	Not measured	2.87 days in aminophylline group vs. 2.69 days in placebo p=0.53	Statistically significantly higher rates of Nausea, vomiting in aminophylline group p=0.05, no statistically significant differences in headache, irritability, tremour or seizures Patients on aminophylline were more likely to have their infusions stopped because of adverse effects	FEV1 @ 24 hours 22.5 in aminophylline vs 13.1 in placebo p=0.029

Table 7. Results of observational studies

First author, Location, age range of participants	Study design	Timing of theophylline level measurement	Theophylline levels achieved	Time until resolution of symptoms	Need for mechanical ventilation	Date until discharge criteria are met	Actual discharge	Adverse effects	Spirometry
Fox 1982{Fox 1982}, USA,1-16 years	Retrospective analysis of patients' theophylline levels on subsequent therapeutic decisions	Not measured	<10mg/l in 20 patients 10-20mg/l in 14 patients, no patients had levels >20mg/l	Not measured	Not measured	Not measured	3.25 days	3 patients with theophylline levels 20.5mg/l, 21.1mg/l and 25.6mg/l non showed signs of theophylline toxicity	Not measured
Dalabih 2014{Dalabih 2014}, USA, 3-18 years	Retrospective analysis of critical care patients admitted with an acute exacerbation of asthma were compared with similar patients who did not	Not measured	31 had theophylline levles≥10mg/l, 18 had theophylline levels≤10mg/l	Time to reach RDS*≤7 longer in those who received aminophylline compared to those who did not (HR=0.359 95% CI [0.223, 0.578] p<0.001. Longer in those with levels 10-20mg/l HR=0.403 CI [0.204, 0.739] p=0.008	Not measured	Not measured	Aminophylline associated with longer stay in critical care HR=0.396 CI[0.245, 0.64] p<0.001. Among those who receive aminophylline length of stay was longer HR=0.457 CI [0.234, 0.895] p=0.023	Not measured	Not measured

RCT randomised controlled trial, CAS/PI clinical asthma score/pulmonary index, ASS asthma severity score, RDS respiratory distress score

2.3.4 Theophylline levels

For the 10 RCTs, six gave an optimal therapeutic range for theophylline: three studies aimed for serum concentrations between 10 and 20mg/l [90,94,96] one study of 15mg/l [98], one between 12-17mg/l [99] and one between 12-20mg/l [92]. Of the observational studies, one defined target therapeutic levels as 10mg/l or greater [100] and one as 10-20mg/l [101].

There was non-uniformity in the timing of theophylline level measurement. Of the randomized controlled trials, three measured serum levels 30 minutes after completion of the loading dose [90,97,98], three after one hour of completion of the loading dose [94,95,99], and one six hours after completion of loading dose [92]. The timing of serum measurement was not reported in one RCT and neither observational study [91,100,101]. Serum levels were measured in all participants receiving theophylline, except in one study, where only 17% of those in the intervention group had serum theophylline levels measured [91].

There was heterogeneity between studies in the way in which theophylline levels were reported. Five studies presented the mean theophylline level achieved [91,92,96,97,100], three gave the proportion of research participants who were below/above the target range [95,100,101] and four gave the range of theophylline levels achieved [90,93,94,98].

2.3.5 Primary Outcomes

1) Time until resolution of symptoms. Of the ten RCTs, two reported time until resolution of symptoms as an outcome [92,99], four measured change in asthma score over a given time [90,94,96,98], and four did not measure symptoms. Various symptom scores were used (Table 4).

There appeared to be no difference in the magnitude of results when comparing levels of serum theophylline measured in participants. One RCT demonstrated that symptom improvement was quicker in those receiving theophylline compared with placebo (18.6±2.7h vs 31.1±4.5h [$p<0.05$], mean serum theophylline levels 11.2mg/l) [99] but this was not replicated in another study in which similar serum theophylline levels were reported (30.4±16.8h vs 27.0±10.3h [$p=0.51$], mean serum theophylline level 13.1mg/l) [92]. No studies demonstrated a statistically significant improvement in symptoms after 2, 6, 12, 24, 48 and 36 hours at any serum theophylline level [90,94,96-98].

One retrospective study measured time until symptom improvement and found that this appeared to be longer after treatment with aminophylline (hazard ratio 0.359, $p<0.001$). The authors also note that this was significantly more prolonged in those with levels >10mg/l compared to those who are subtherapeutic (hazard ratio 0.403 $p=0.0085$) [100].

2) Need for mechanical ventilation. No studies compared the effect of IV aminophylline against placebo, in non-intubated children, on the subsequent need for mechanical ventilation.

3) Mortality. There were no reported deaths in any study.

2.3.6 Secondary outcomes

1) Date until discharge criteria are met. One study reported time until children were ready for discharge home and found no significant difference between theophylline and placebo (27.0±10.3 hours vs 30.4±16.8 hours [p>0.05] mean theophylline level 13.1mg/l) [92]. Another study measured time to meet discharge criteria from the intensive care unit, but not time until discharge home. The study reported a statistically significant difference in favour of aminophylline (29.8±4.9h vs 36.4±5.5h [p<0.05]. Mean daily theophylline level 14.5±0.7 mg/L, target theophylline levels 12-17mg/l) [99].

2) Actual discharge. Four studies recorded length of time in hospital as an outcome. One study, in which mean theophylline levels were 7.2mg/l [91] and one study with mean levels of 12.3mg/l [95] demonstrated no statistically significant difference in length of hospital stay when compared to placebo. One trial demonstrated a significant improvement in length of stay in critical care in the aminophylline group compared with placebo (3.9±0.3 days versus 8.8±1.5 days in placebo [p<0.05] mean serum theophylline level 11.2mg/l), but not in discharge home (8.3±1.5 days versus 13.0±1.0 days [p>0.05]

mean serum theophylline level 11.2mg/l). This study demonstrated a significantly shorter length of stay in critical care in the very small subset of intubated patients receiving aminophylline compared to those receiving placebo [99].

One retrospective study found that length of stay in critical care was longer for subjects receiving aminophylline (hazard ratio 0.396, [p=0.001], 63% of participants >10mg/l) but does not follow up patients until discharge home. Of those receiving aminophylline, those found to have levels >10mg/l had a longer stay in the intensive care unit compared to those who with levels <10mg/l [100]. Another retrospective study reported the mean length of stay of hospital for patients receiving aminophylline was 3.25 days, however no comparison is made between those achieving different serum theophylline levels [101].

3) Adverse effects. Eight RCTs reported adverse effects. Three studies demonstrate statistically significantly higher rates of adverse effects in those receiving intravenous theophyllines compared to placebo [95-97] whilst another study showed no significant difference [94]. In the few research participants with supratherapeutic theophylline levels (>20 mg/l) there did not appear to be an increased risk of side effects. One retrospective study reported no adverse effects in any of its supratherapeutic patients [101], and one study linked adverse effects to an individual participant who experienced nausea and abdominal pain with levels of 23mg/l [97].

4) Spirometry. Three studies reported FEV_1 as an outcome. Two studies demonstrated significant improvements in FEV_1 in the theophylline group compared to placebo (22.5 vs 13.1 [p=0.029], serum level of participants 10-20mg/l) [94] (89 vs 62 [p<0.001], serum level of participants 5-15mg/l) [93] whilst another study with theophylline levels between 10-20mg/l demonstrated no statistically significant difference in FEV_1 [98]. In other studies, a large proportion of participants were unable or unwilling to perform spirometry.

2.4 Discussion

There is no evidence to suggest that 10-20 mg/l of theophylline is the optimal target serum range in children with severe acute asthma. Across studies comparing aminophylline to placebo there appears to be no difference in symptom resolution between children with serum theophylline concentrations between 10-20mg/l, and those under 10mg/l. There is no evidence to suggest serum concentrations within the therapeutic range reduce the need for mechanical ventilation or mortality. There is weak evidence to suggest that levels over 20 mg/l are associated with an increase in abdominal pain, nausea and vomiting.

The principles of TDM are based upon a correlation between serum drug concentrations and clinical outcomes. This review demonstrates that there is an unclear relationship between serum levels and either clinical efficacy or development of adverse effects. Until there is clear evidence that the beneficial serum level of theophylline lies within a certain range, rigorous evaluation of clinical progress and adverse drug effects should be used to guide therapy rather than laboratory investigations.

Data from one study suggests that a 5mg/kg loading dose would leave one third of children below 10mg/l, and none above 20mg/l [102]. Routine measurement of serum theophylline levels in children suffering acute asthma who have received standard loading doses of aminophylline to achieve serum concentrations in the 10-20mg/l range is therefore unlikely to result in any clinical benefit or reduction in adverse effects. However measurement of serum theophylline in childhood acute severe asthma may still retain utility in the assessment of patients in whom there is concern about overdose.

As we were unable to identify any RCTs directly comparing target ranges of theophylline, our analyses incorporate indirect observational comparison across studies. For an evidence based therapeutic range to be determined, there is a need for RCTs comparing ranges and measuring important clinical outcomes, to determine the optimal dose in children.

Many included studies measured outcomes that are poor reflections of patient improvement, and there was poor reporting of the results of TDM across studies [66]. Furthermore, our included studies span a 43 year time period and changes clinical practice, administration of IV aminophylline and the selection of outcomes present further challenges when comparing results. All of these issues contribute to data heterogeneity. Meta-analysis was considered but is unlikely to provide further insight into the optimum therapeutic range of aminophylline.

Research in children presents specific challenges such as potential difficulty in reporting subjective side effects and reluctance to take blood samples, so monitoring of adverse effects may be difficult. We agree with the need for consistent reporting of adverse effects in clinical trials [89]. A core outcome set is needed to measure and report outcomes in all trials. This should be developed using rigorous consensus methodology [66] and would help interpretation of studies, enable synthesis across trials, and reduce reporting bias [65].

2.5 Conclusion

There is no evidence that theophylline levels above 10mg/l compared with levels below 10mg/l are associated with improvement in children with severe acute asthma, nor that levels below 20mg/l are associated with fewer adverse effects than higher levels. Even if theophylline levels are measured, we recommend that clinicians should be guided by clinical improvement, and be

vigilant to adverse effects, rather than simply titrate the dose according to serum levels. Randomized controlled trial evidence comparing two therapeutic ranges may provide further information on the optimum serum concentrations of intravenous aminophylline. These should measure and report a standardized core set of validated outcome measures reflecting both benefits and harms.

2.6 Summary

The optimum monitoring practices of intravenous aminophylline are not known. This chapter aimed to assess whether serum theophylline levels between 10-20mg/l are associated with superior clinical asthma outcomes in children. A systematic review found a poor evidence base for the current therapeutic range. As the results of TDM are factored into aminophylline dosage, alternative prescribing practices may benefit children suffering an exacerbation of asthma. An enquiry into the optimum dosing regimen of aminophylline is an important stage in assessing the evidence for current aminophylline recommendations.

Chapter 3: A Systematic Review of Aminophylline Dosage

3.1 Background

3.1.1 Safe Prescribing

Aminophylline prescribing practices should reflect the maximum safety and efficacy profile of the drug. Inappropriate dosage can result in toxicity from an overdose, or therapeutic failure if dosage is too small. This may prolong an acute exacerbation of asthma resulting in significant harm to children. When prescribing aminophylline to children, serum theophylline concentrations are incorporated into dosage calculations [30,44]. As serum theophylline levels were shown to be a poor predictor of efficacy of safety and efficacy in Chapter 2, an alternative dosing strategy may help maximize the benefit of intravenous aminophylline.

Safe and effective prescribing of aminophylline requires an understanding of its pharmacological properties. Cardiac arrhythmias and seizures are potentially fatal consequences from aminophylline overdose [73-75], whilst other adverse effects such as nausea and vomiting are extremely distressing in the context of an acute exacerbation of asthma. Interindividual variation in clearance rates mean that a dose that is toxic in one patient may not provide adequate treatment in another. Safe dosing is further complicated its

purported narrow therapeutic range (Chapter 1).

3.1.2 Dosage Calculations

A loading dose is an initial higher dose of a drug that may be given at the beginning of a course of treatment to rapidly achieve therapeutic levels [103]. The half-life of aminophylline is long and treatment may be commenced with a loading dose to hasten its anti-asthmatic action. Once the desired serum levels have been achieved following loading, a maintenance infusion is administered. This is a lower dose of the drug intended to maintain aminophylline serum concentrations within the therapeutic range. Once steady state has been achieved, the rate of drug administration should be equal to elimination to keep serum concentrations constant. Not all children receive loading doses, such as those who take oral theophylline regularly (Chapter 1). Calculating aminophylline doses aiming for a therapeutic level requires knowledge of aminophylline disposition the optimal therapeutic level in children suffering an exacerbation of asthma (Fig 7).

Fig 7. Dosage calculations for intravenous aminophylline

$$Loading\ dose = \frac{C_p V_d}{FS}$$

C_p = Desired serum concentration of the drug
V_d = Volume distribution of the drug
F = Bioavailability
S = Salt factor

$$Maintenance\ dose = \frac{C_p CL}{F}$$

C_p = Desired serum concentration of the drug
CL = Clearance of the drug in body (L/h)
F = Bioavailability

Volume distribution: the theoretical volume that would be necessary to contain the total amount of an administered drug at the same concentration that it is observed in the blood plasma
Bioavailability: the fraction of an administered dose of unchanged drug that reaches the systemic circulation
Salt factor: the fraction of the administered dose, which may be in the form of an ester or salt, that is the active drug.

Data on the optimum loading dose of aminophylline to use in children are conflicting and inconsistent. A loading dose of 5.6mg/kg has been calculated based on pharmacokinetic data of ten children aged between 1-4 years designed to achieve a concentration of 10mg/l [104]. In practice, a loading dose of 5mg/kg has been shown to be ineffective at achieving levels between 10-20mg/l in around 30% of children [102]. A higher loading dose of 6mg/kg has been shown to achieve serum theophylline levels between 10-20mg/l in all children (n=11) [105], however this is inconsistent with more recent data [106]. These represent an early rationale for drug doses, but are underpowered and unable to account for the differing pharmacokinetic parameters across children of different ages.

A lack of evidence is also seen in the recommended doses for maintenance doses of aminophylline. The rate of administration should equal the rate of elimination, however this is highly variable in a population. As younger children are purported to eliminate theophylline at a faster rate than older

children and adults [11], those under 12 receive infusion rates of doses of 1mg/kg/hr, compared with 0.5mg/kg/hr in children over 12. To account for the individual variation in clearance rates, infusion are then adjusted based on the results of therapeutic drug monitoring. There is little data to suggest that children receiving aminophylline maintenance infusions achieve constant theophylline serum concentrations, or if these adjustments based on age represent the optimal dose of aminophylline.

Chapter 2 did not show clear serum concentration at which aminophylline is most effective and pharmacokinetic studies alone would not be unable to guide optimum dosage. Instead, understanding the relationship between dose and outcome is required.

3.1.3 Aim

This chapter aims to investigate the correlation between aminophylline doses and clinically relevant outcomes.

3.2 Methods

3.2.1 Study Design

We conducted a systematic review of studies utilizing intravenous theophyllines in the management of asthma exacerbations in children in order to evaluate the optimum dosing strategy of intravenous aminophylline.

3.2.2 Included Studies

The lack of primary research investigating the optimum dosages of drugs in children has been recognised [107]. Similar to the review question in Chapter 2, the practical and ethical challenges faced when investigating aminophylline use in children means our methodology must account for the high probability of few primary studies directly investigating dosage. Therefore, we used a systematic review technique that anticipates various study designs, similar to the previous chapter. This systematic review technique has been used to assess the dosage of methotrexate [108]. We decided a priori that the most relevant study type would be a comparison of randomised controlled trials (RCTs) comparing different dosing strategies and measuring clinically relevant outcomes, but we would also include RCTs evaluating the efficacy of intravenous theophyllines compared with placebo or other treatment, with subsequent analyses performed for each comparator drug, and observational studies.

We included studies that investigate the efficacy of intravenous theophyllines in children suffering an exacerbation of asthma if the dosing regimen was reported. We excluded studies performed in adults, those utilizing theophyllines for indications other than asthma or studies using non-intravenous routes.

3.2.3 Outcomes

Our selected outcomes were the same as those in Chapter 2. Primary outcomes were i) time until resolution of symptoms, ii) need for mechanical ventilation, and iii) mortality. Secondary outcomes were i) the number of days until discharge criteria are met, ii) number of days until actual discharge from hospital and iii) adverse effects as defined and reported by authors.

3.2.4 Identification of studies

The following search strategy was used to search MEDLINE, CINAHL, The Cochrane Central Register of Controlled Trials, and Web of Science in March 2016 with no date or language restrictions:

asthma* AND (emerg* OR acute OR severe* OR intensive* OR exacer bation OR critical OR refractory OR hospitali*ed OR attack OR status) AND (aminophylline* OR intravenous theophylline* OR xanthin* OR m ethylxanthin*) AND (child* OR adolescent* OR infan* OR p*ediatric)

Reviewer LC screened titles and abstracts, a second reviewer (IS or DH) checked the eligibility of abstracts after initial screening, and full studies included in the review. Reference lists were screened for other eligible studies.

3.2.5 Assessment of risk of bias

The Cochrane Risk of Bias Tool was applied to each RCT. If a dosing regimen was found to demonstrate a superior dosing regiment we used this tool to help determine the validity of results.

3.2.6 Data extraction and analysis

From each study we extracted the loading dose and/or maintenance dose of IV theophyllines administered, and whether subsequent doses were adjusted based on the results of therapeutic drug monitoring. The age range, number of participants and use of concomitant medications was also extracted.

If possible, we intended to conduct a quantitative synthesis by pooling studies utilizing similar dosing regimens. Separate meta-analyses for each dosing regimen used would allow for a quantitative comparison of effect size between studies. If quantitative techniques were not possible due to methodological or reporting heterogeneity, or insufficient data, we planned for a descriptive analysis correlating pre-specified clinical outcomes to the dosing strategies used.

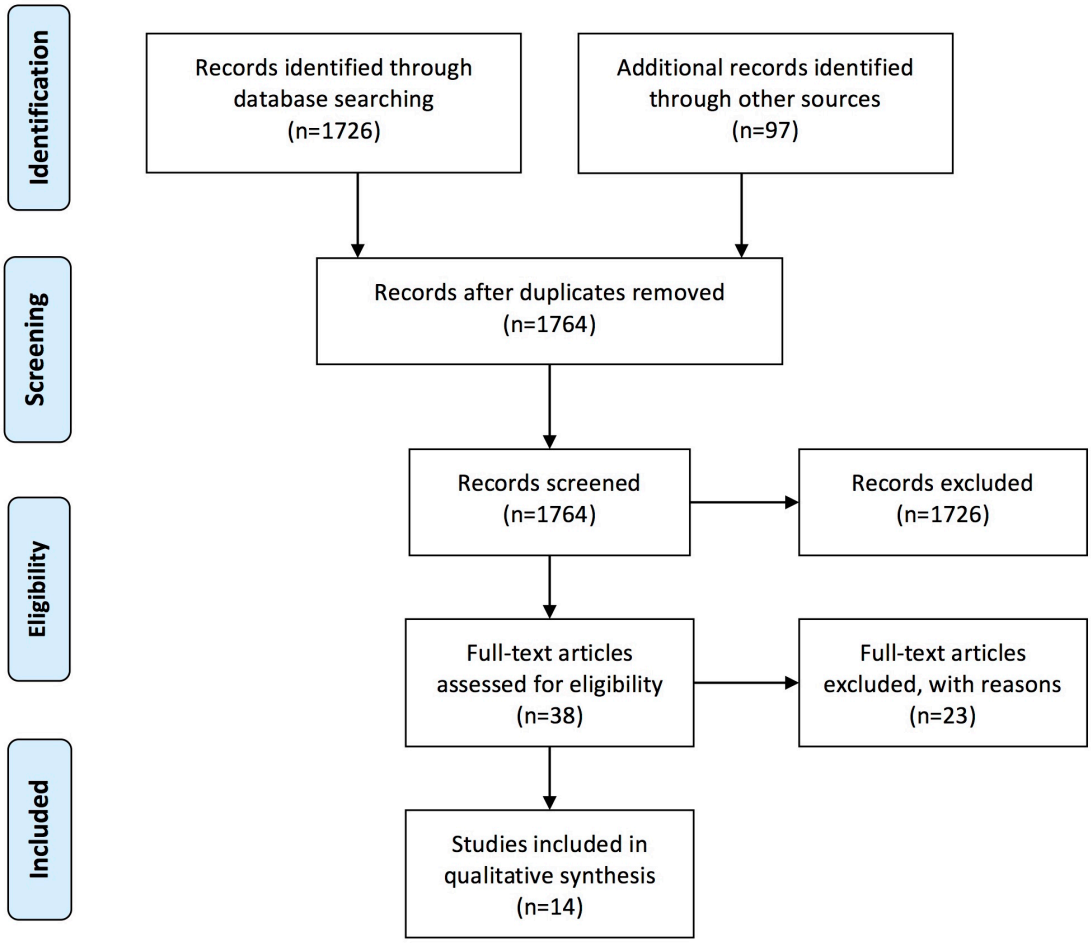
3.3 Results

3.3.1 Included Studies

Our search strategy returned 1764 studies, with 38 full text articles assessed for eligibility. We excluded 23 full text articles (appendix) with the remaining

14 studies included in this systematic review (Fig 8).

Fig 8. Search results of the systematic review investigating aminophylline dosage



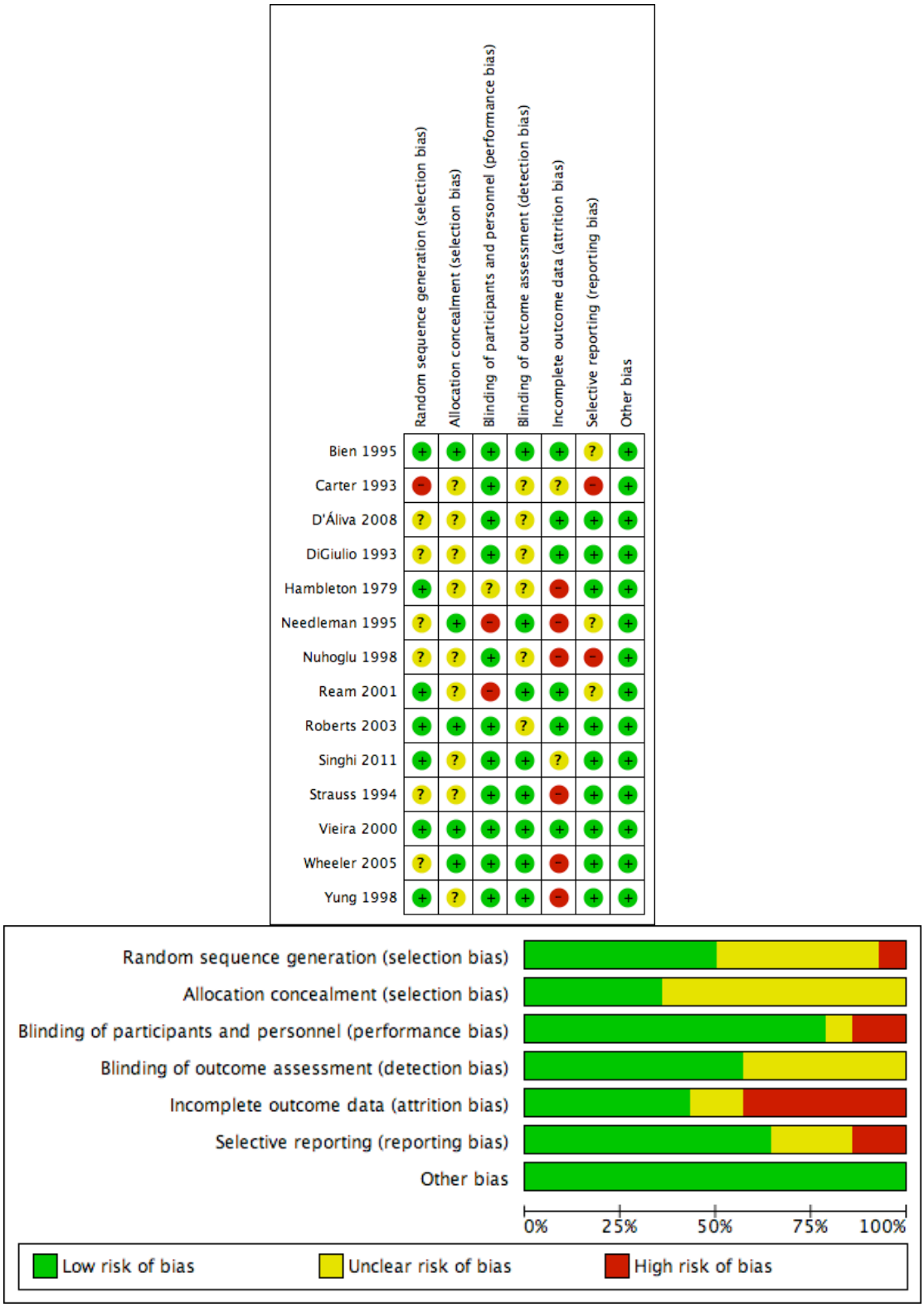
No RCTs comparing dosing strategies for IV aminophylline in children suffering an exacerbation of asthma were identified. We therefore included 14 RCTs comparing aminophylline to placebo (n=10) or β_2 adrenergic agonists (n=4).

3.3.2 Risk of Bias of Included Studies

The results from the Cochrane risk of bias assessment are shown in Fig 9. A high risk of selection bias was found in one study [98], performance bias was found in two studies [90,99], attrition bias in six studies

[90,94,95,97,109,110] and reporting bias in two studies [94,98]. All other domains were found to have a low or unclear risk of bias.

Fig 9. Results of assessment of risk of bias of included studies investigating the optimum dosage of intravenous aminophylline in children



3.3.3 Study Characteristics

Studies were grouped based on whether they compared aminophylline to placebo or β_2 adrenergic agonist. The loading doses, maintenance doses and clinical outcomes are shown in Tables 1 and 2

Table 8. Results of RCTs comparing aminophylline to placebo

Author, number of participants (intervention vs control)	LD	I	Symptom resolution	Intubation	Discharge criteria	Actual Discharge	Adverse effects
Yung 1998, 81 vs 82	10	0.7 to 1.1	Not reported	Not reported	Not reported	2.87 days vs. 2.69 days in p=0.53	Higher rates of nausea and vomiting but not headache, irritability and tremor
Needleman 1995, 22 vs 20	6-8	0.8 to 1	Change in ASS 6.96±1.65 vs 7.00±1.73 to 3.05±3.25 vs 2.38±2.19 [p=0.482]	Not reported	52.3±32.3 hours vs 48.2±26.6 hours p=0.654	Not measured	Not reported
Strauss 1994, 14 vs 17	7	0.75 to 1.2	Not reported	Not reported	Not reported	2.58±1.5 days vs 2.33±1.3 days p>0.2	Higher rates of side effects in intervention vs aminophylline group 6/14 (43%) vs 1/17 (6%) in control p<0.05
Ream 2001, 23 vs 24	7	0.5-0.8	Time to reach CAS<3 18.6±12.0 h vs 31.1±20.1 h; p=0.0238	All subjects intubated before infusion	29.8±21.9h vs 36.4±25.9h p=0.3774	4.7±1.3 days vs 5.1±1.8 days p=0.432	No significant difference between intervention and control
Nuhoglu 1998, 18 vs 20	6	0.8 to 1.0	Clinical asthma score at 24 hours in intervention vs placebo 2.05±1.61 vs 1.94±1.78 p=0.8452	Not reported	Not reported	Not reported	NO significant difference between intervention and control

Author, number of participants (intervention vs control)	LD	I	Symptom resolution	Intubation	Discharge criteria	Actual Discharge	Adverse effects
Vieira 2000, 24 vs 19	6	1.2	Time to reach Wood-Downes score ≤ 2 12.5h vs 14.6h in p=0.13	Not reported	Not reported	12.5h vs 14.6 h p=0.13	No serious adverse events in either group
DiGiulio 1993, 16 vs 13	6	0.85 to 1.0	Time to reach asthma score <2 in intervention vs control 30.4±16.n vs 27.0±10.3 p = 0.51	Not reported	30.4±16.8h vs 27.0±10.3h p = 0.51.	N/A	No significant difference between intervention and control
D'Avila 2008, 30 vs 30	5	None	Not reported	Not reported	Not reported	43.2±3.30h vs 43.6±23.7h p=0.95	Not reported
Carter 1993, 12 vs 9	TDM*	0.8 to 1.0	Median CAS/PI at 36 hours 2.0 vs 2.0 p>0.05	Not reported	Not reported	3.5±2.5 days vs 3.0±1.5 days p=??	No significant difference between intervention and control
Bien 1995, 19 vs 20	5*	0.9	CAS 24 hours in intervention vs control 2.0 vs 2.6 p>0.05	Not reported	Not reported	Not reported	Higher rates of nausea and emesis in theophylline group p≤0.05 but not insomnia p=0.08

*Doses calculated based on the results of therapeutic drug monitoring. ASS asthma severity score, CAS/PI clinical asthma score/pulmonary index, LD loading dose (mg/kg), I infusion rate (mg/kg/hr)

Table 9. Results of RCTs comparing aminophylline to β_2 adrenergic agonist.

Author, number of participants (intervention vs control)	LD	I	Symptom resolution	Intubation	Discharge criteria	Actual Discharge	Adverse effects
Wheeler 2005, 13 vs 27	6.4	0.64 to 0.96	Time to reach CAS ≤3 24.2±12.1h vs 51.6±33.3h p<0.05	No patients required mechanical ventilation	Not measured	Not reported	NS in the median number of adverse effects, higher incidence of nausea in combined group
Roberts 2003 , 26 vs 18	5	0.9	Change in ASS over 2 hours -1.19±1.3 vs -1.11±1.7 p=0.85	1/26 vs 2/18 in salbutamol p>0.05	Not measured	Time to discharge in aminophylline vs salbutamol 57.3h±43.3 vs 85.4h±56.0 p=0.02	Adverse effects In aminophylline group vs salbutamol 22.2% vs 36% p=0.50
Singhi 2011, 33 vs 66	5	0.9	number of participants with improvement in CAS at 1h ≥4 am, ter, 5 vs 5 p=0.002	Not reported	Not measured	Not reported	None in Mg group, 2 patients in terbutaline group had hypokalaemia and 9 in am group had nausea/vomiting
Hambleton 1979, 9 vs 9	4	0.6	Change in asthma score at 24 hours 4.5 vs 4.0 in p>0.05	Not reported	Not reported	Not reported	Higher rates of tachycardia in salbutamol group

ASS asthma severity score, CAS/PI clinical asthma score/pulmonary index,. LD loading dose (mg/kg), I infusion rate (mg/kg/hr)

3.3.4 Aminophylline doses

The doses given to children across RCTs utilizing IV aminophylline for an acute exacerbation of asthma in children is highly variable. All but one study [91] prescribes aminophylline as a loading dose followed by an infusion. All studies calculate doses based on the actual weight (rather than optimal weight) of individual participants, it is not clear in any study whether these were based on actual weight, estimated weight or ideal weight of a child. Loading doses range from 4-10mg/kg and infusion rates range from 0.5-1.2mg/kg/hr.

Age was factored into dosing strategies of aminophylline in eight studies. Age influenced both the loading dose and the infusion rate given in one study [90], with the remaining seven studies using age adjusted maintenance doses only [91,92,94,95,97,99,109]. In most studies, younger patients received higher doses of IV aminophylline.

The results of therapeutic drug monitoring (TDM) factored into aminophylline dosage calculations in the majority of studies. Infusion rates were adjusted based to keep serum theophylline levels within a predefined range in nine studies [90,92,94-98,109,111]. In two studies [96,98] serum theophylline levels were factored into loading dose calculations.

3.3.5 Primary Outcomes

1) Time until resolution of symptoms Symptom resolution was reported in seven studies comparing aminophylline to placebo. Asthma score after a given time was reported in four studies [90,94,96,98] and time to reach a predefined asthma score was reported in three studies [92,99,112]. All four studies comparing aminophylline to β_2 adrenergic agonist reported symptom resolution as an outcome. This was reported as time to reach a predefined asthma score in one [109], change in asthma score in two [110,111] and the proportion of patients in each group achieving a low asthma [113].

There appeared to be no discernible relationship between aminophylline dosage and improvement in symptoms. Although one study reported quicker improvement in asthma score with a loading dose of 7mg/kg followed by an infusion of 0.5-0.65mg/kg/hr (time to reach CAS≤3 in aminophylline vs placebo group 18.6±12.0 h vs 31.1±20.1 h; [p=0.0238]) [99], this finding is not replicated in studies using similar doses despite similar patient cohorts [90,92]. Intravenous aminophylline at any dose was equally effective when compared to β_2 adrenergic agonist at improving symptoms. Due to the differences in methodologies of measuring symptoms, statistical pooling of data for time until resolution of symptoms was not possible.

2) Need for mechanical ventilation. No studies comparing aminophylline to placebo assessed effect of IV aminophylline against placebo, in non-intubated children, on the subsequent need for mechanical ventilation. One study comparing a 5mg/kg loading dose followed by an infusion of 0.9mg/kg/h to β_2 adrenergic agonist,

found a that one subject in the aminophylline group and 2 in the β_2 adrenergic agonist group required mechanical ventilation [p>0.05] [111] however it is not possible to compare this finding with other doses given.

3) Mortality. There were no reported deaths in any study

3.3.6 Secondary outcomes

1) Time until discharge criteria are met. Time until discharge criteria are met was reported in three studies comparing aminophylline to placebo, one using a 7mg/kg loading dose followed by an infusion of 0.5-0.8mg/kg/hr [99] and one using a 6mg/kg loading dose followed by an infusion rate of 0.85-1.0mg/kg/hr [92], and one adjusting loading and maintenance doses based on age [89]. No studies reported a significant improvement in time until discharge criteria are met with the use of intravenous aminophylline at any dose. One study reported an improvement in the very small subset of patients who were intubated prior to enrolment 74.8±15.4 in theophylline group vs 189.3±59.8 in control p=0.0325 [99].

2) Actual discharge. Length of stay was reported in five studies comparing aminophylline to placebo [91,95,97-99] and one study comparing aminophylline to β_2 adrenergic agonists [111]. Four studies reported the number of days spent in hospital [95,97-99] one study reported the number of hours spent in the paediatric emergency room, [91] and one study reported the number of hours spent in hospital [111]. No statistically significant difference was observed in shortening hospital length of stay at any dose of aminophylline when compared with placebo. A loading

dose of 5mg/kg followed by an infusion of 0.9mg/kg/h was shown to significantly shorten hospital stay compared with β_2 adrenergic agonist (57.3h±43.3 vs 85.4h±56.0 [p=0.02]) [111].

3) Adverse effects. Adverse effects were compared in six studies comparing aminophylline to placebo [92,94-98] and no studies comparing aminophylline to β_2 adrenergic agonist.

There appears to be a higher rate of adverse effects (nausea and vomiting in particular) in participants receiving higher loading doses. A significantly higher rate of adverse effects was reported in two studies using a loading dose of 10mg/kg and 7mg/kg [95,97] but not in studies using loading doses between 5-6mg/kg [91,93,98,117]. One study reported a higher rate of adverse effects in subjects receiving a loading dose calculated using 500ml/kg X change in serum level formula [96].

3.4 Discussion

We found no correlation between dosage of intravenous aminophylline in and symptom resolution in children suffering an acute exacerbation of asthma. We did not identify any studies that assessed the effect of aminophylline on the need for mechanical ventilation or mortality. There is no correlation between dose and length of stay, and there is weak evidence to suggest that loading doses above 7mg/kg result in a higher rate of nausea and vomiting. There is no evidence to indicate that adjustment of dose based on age or serum theophylline levels increases the efficacy

or safety of IV aminophylline.

No RCTs have directly compared dosing strategies for aminophylline when used for acute asthma exacerbations in children. The indirect evidence from RCTs comparing aminophylline with placebo demonstrates no clear relationship between dosage regimen, which varies across studies, and clinical efficacy and safety. The majority of dosing strategies aim to achieve serum theophylline levels within a predefined range, but this did not translate into clinical improvement.

Forming dosing recommendations for IV aminophylline in children is complex as the drug is used in a wide age range of children with highly variable pharmacokinetic properties. Although efforts to account for this variability are reflected in dosing adjustments made for age, weight and previous theophylline levels, it is unclear whether these adjustments play a significant role in improving the clinical outcomes of children with acute asthma. Dosing strategies based on evidence of clinical improvement are an important factor when comparing the efficacy of intravenous bronchodilators for the treatment of childhood asthma. There is a need for research linking the pharmacokinetic knowledge of theophylline, with clinically relevant outcomes in acute asthma in children.

The available data on which to base aminophylline dosage in children are sparse. Pharmacokinetic studies allow for the calculation of important parameters in calculating drug dose, by observing serum drug concentrations achieved and rates of elimination. Study designs commonly used in adults are not transferable to the paediatric population [78] and few pharmacokinetic studies investigating aminophylline disposition are conducted in children due to ethical limitations,

practical challenges and a smaller pool of eligible participants. Asthma is a medical emergency, which presents technical challenges in undertaking accurate pharmacokinetic studies of aminophylline in sick children. Lower financial incentives are a further barrier as the cost of conducting research in children is likely to exceed profits [45]. Theoretical dosage calculations based on pharmacokinetic studies are vulnerable to large oversimplifications, and cannot adequately account for the high interindividual variation in theophylline clearance. The few Pharmacokinetic studies investing aminophylline dosages in children use serum theophylline levels as an endpoint [104-106]. This has been shown to correlate poorly with outcomes in Chapter 1. Future work must measure clinically relevant outcomes when investigating optimum doses of aminophylline in children.

As no RCTs compare aminophylline doses in acute asthma, this review is hindered by its use of indirect evidence. This study was unable to provide quantitative effect sizes using meta analysis techniques due to a heterogeneity in reporting and a lack of data. Furthermore, this review included studies spanning a 32 year time period, and it is not clear whether administered doses of aminophylline where based on ideal, estimated or actual weight. Additionally, intravenous theophylline and aminophylline (theophylline with ethyldiamine) were considered together.

3.5 Conclusion

The optimum dosing strategy for IV aminophylline for children suffering an acute exacerbation of asthma is unclear. The recommended 5mg/kg loading dose followed

by an infusion of 0.5-1.0mg/kg/hr with adjustments made based on serum theophylline levels may not reflect the optimum efficacy of the drug. Appropriate paediatric dosage calculations for aminophylline may require adjustments for age, weight and previous serum theophylline levels. Pharmacokinetic studies and high quality randomised controlled trials comparing dosing strategies are needed to improve the provision of IV aminophylline.

3.6 Summary

As TDM was shown to be a poor predictor of efficacy in Chapter 2, this work aimed to investigate a correlation between dosage and outcomes. This systematic review found a poor correlation between dose and efficacy. Indirect evidence was used in data synthesis as no studies directly comparing doses were identified. As serum theophylline levels, dosages prescribed and clinical outcomes are routinely measured in clinical practice, a prospective analysis which links both therapeutic drug monitoring practices (Chapter 2), dosage (Chapter 3), with clinical outcomes may provide further answers on how to maximise the efficacy and safety of intravenous aminophylline.

Chapter 4: Pharmacokinetics and clinical outcomes of children receiving intravenous aminophylline for an exacerbation of asthma

4.1 Background

4.1.1 Linking TDM, Dosage and clinical outcomes

Previous chapters have found a poor correlation between serum theophylline levels, aminophylline dosage and clinically relevant outcomes (Chapters 2 and 3). Current research is unable to provide a definitive dosage and monitoring strategy, which results in superior outcomes to those recommended in clinical practice. Complex guidelines govern the provision of intravenous aminophylline in children (Fig 3, Chapter 1) and it is not clear whether these represent optimum prescribing practices, or even whether these are followed in clinical practice.

Patients who receive intravenous aminophylline are subject to therapeutic drug monitoring following the administration of loading doses, and at regular intervals during intravenous infusions. When a hospitalized child requires intravenous aminophylline for an asthma exacerbation, the results of therapeutic drug monitoring and the dosage of aminophylline prescribed are stored on hospital databases. This practice generates child specific pharmacokinetic data in a method that does not affect clinical care, or subject children to unnecessary risks associated with traditional PK studies [45,114]. A prospective investigation that considers

theophylline levels, dosage and clinical outcomes together can be used to develop findings from previous Chapters 2 and 3.

4.1.2 Aim

This chapter is an audit aiming to investigate whether the guidelines outlined in Chapter 1 are followed. We will also assess whether children achieve serum concentrations between 10-20mg/l and whether children in this range have superior asthma outcomes.

4.2 Method

4.2.1 Study Design

We performed a prospective audit of aminophylline usage. Children were eligible if they received intravenous aminophylline for an acute exacerbation of asthma at Alder Hey Children's Hospital. We excluded children who were prescribed aminophylline for other indications. Hospital computer systems were used to extract relevant pharmacy data, including dose of aminophylline administered, serum theophylline levels achieved and timing of measurement. This study was registered with the clinical audit department, Alder Hey.

4.2.2 Prescribing Practices

We assessed whether clinicians followed the 2014 Alder Hey prescribing guidelines (Chapter 1 fig 4). If a loading dose was required, we assessed whether a 5mg/kg bolus was administered, and whether an age appropriate infusion rate was

prescribed. We recorded whether children received concomitant intravenous salbutamol or magnesium sulphate.

4.2.3 Serum theophylline levels

We aimed to investigate whether current prescribing practices achieve the purported therapeutic range of 10-20mg/l. We collected the serum theophylline levels of children post loading and the number of children requiring top up loading doses. We also assessed whether serum levels were measured at the correct time.

4.2.4 Clinical outcomes and adverse effects

We compared the outcomes of children with levels between 10-20mg/l with those who were sub/supratherapeutic. Our chosen outcomes were days until salbutamol was commenced at five puffs four hourly, days until discharge and days until in room air. We also collected data on common adverse effects including hypokalaemia, nausea, vomiting, hypoalbuminaemia, tremor and electrocardiogram (ECG) changes. Serum levels of children who experienced at least one adverse effect were compared with children who suffered no adverse effects.

4.3 Results

4.3.1 Participants

Complete data were available for 28 children between July 2014 and April 2016 with an average age of 10.3±5.0 years. Over this period, two patients had multiple

admissions, one patient was admitted ten times and one patient admitted twice, hence there are 38 admissions in total.

4.3.2 Prescribing practices

All of the 17 children who did not take oral theophylline received the correct loading dose of 5mg/kg. The correct initial infusion rates were given in 15 patients (1mg/kg/h if under 12 years, 0.5mg/kg/h if over 12 years). Of the two patients who received incorrect infusions, one was over 12 received an infusion rate of 1mg/kg/hr, and one patient received an infusion rate of 2.5mg/kg/hr. All of these patients attended Alder Hey Children's Hospital only once during this study.

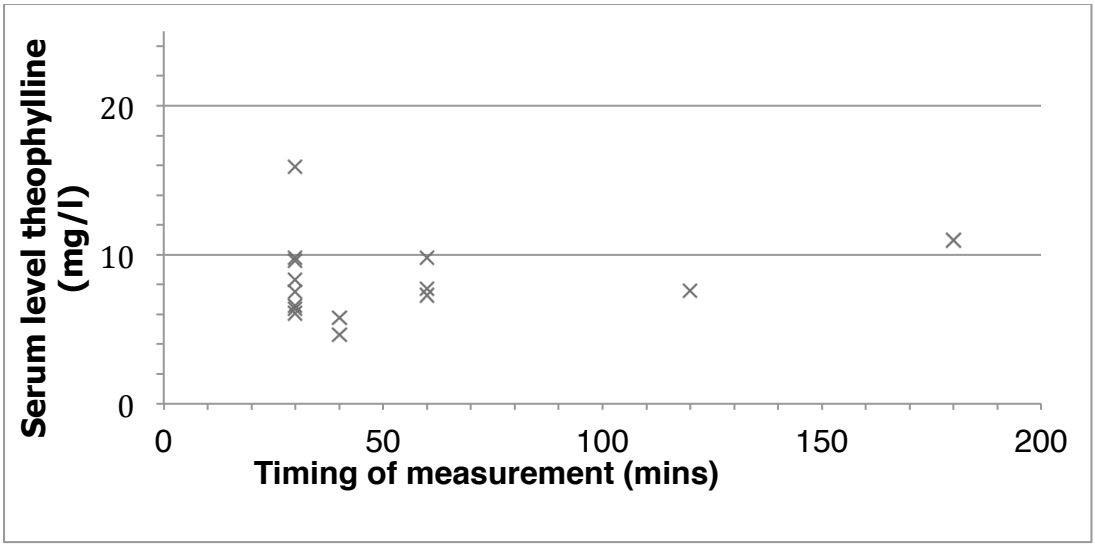
Of the 11 patients who took oral theophylline, 7 required top up loading doses. These ranged between 1mg/kg to 10mg/kg (median 5mg/kg). It is unclear how these top up loading doses were calculated. An incorrect infusion rate was prescribed to 4 (36%) patients. All these errors were due to patients over 12 years of age being prescribed an infusion at a rate of 1mg/kg/hr instead of 0.5mg/kg/hr.
Of 28 children, 22 (79%) received concomitant intravenous magnesium sulphate and 3 (11%) received intravenous salbutamol.

4.3.3 Serum theophylline levels

The average serum theophylline level achieved after a 5mg/kg loading dose was 8.3±2.7mg/kg. Of the 17 patients who received a loading dose, only two achieved levels between 10-20mg/l (Fig 10). Levels were measured at 30 minutes in 7 (41%)

of the 17 patients, with an average post loading measurement time of 53±43 minutes. Serum levels were measured at 12 hours in 12 out of the 17 patients who did not take oral theophylline. Therapeutic levels were achieved in five patients, one patient had levels >20mg/l and six patients were subtherapeutic.

Fig 10. Serum theophylline levels in patients receiving a 5mg/kg loading dose



Each plot represents a patient who received a 5mg/kg loading dose of aminophylline, two patients achieved levels between 10-20mg/l

Of the 10 patients who took oral theophylline, only two patients had serum theophylline levels between 10-20mg/l on admission (13.2mg/l and 15.3mg/l). All other patients had levels below 10mg/l, of the one patient admitted ten times, the median serum concentration on admission was 0.5mg/l.

Of the 16 patients who received top up loading doses, nine achieved serum levels between 10-20mg/l, one patient achieved levels >20mg/l, the remaining patients were subtherapeutic. Of the patient admitted 10 times, the median serum level post

loading was 10.5mg/l (range 7.4mg/l-13.3mg/l). Serum levels were rechecked at 12 hours in 15 patients, 10 patients achieved levels between 10-20mg/l, two patients had levels >20mg/l and three patients had levels <10mg/l.

4.3.4 Clinical Outcomes and adverse effects

A summary of clinical outcomes is shown in table 10

Table 10. Clinical outcomes of children receiving intravenous aminophylline

Outcome	**Result (mean±SD)**
Days in hospital	5.6±9.2
Days until salbutamol five puffs four hourly	3.1±1.5
Days until in room air	2.7±6.2

Aminophylline infusions were stopped in after three hours in 2/28 children. The outcomes of children with maintenance levels >10mg/l at 12 hours were compared with subtherapeutic children. The Mann Whitney U test was performed for statistical significance (table 11).

Table 11. Comparison of outcomes of patients <10mg/l vs >10mg/l

Outcome	**<10mg/l n=6**	**>10mg/l n=20**	**p**
Days until 5 puffs 4 hourly	12.5	16.25	0.336
Length of stay	7.9	15.9	0.039
Days until in room air	19.8	14.6	0.246

Children with levels above 10mg/l did not have superior clinical outcomes compared to children who were subtherapeutic. Children with serum levels <10mg/l had a statistically shorter length of stay compared to those with levels >10mg/l (7.9 vs 15.9 p=0.039).

Adverse effects were experienced in 57% patients of those receiving intravenous aminophylline (Table 12). Hypokalaemia was the most common adverse effect and no patients experienced ECG changes. The average serum level in those with no suspected side effect vs those with side effect was 15.8mg/l vs 17.1mg/l [p=0.69]

Table 12. Adverse effects in children receiving intravenous aminophylline

Side effect	**Frequency (%)**
Hypokalaemia	10 (36)
Nausea/vomiting	7 (25)
Hypoalbuminaemia	3 (11)
Tremor	1 (4)
ECG changes	0 (0)

4.4 Discussion

There is good adherence to the aminophylline dosage and monitoring guidelines for children suffering an acute exacerbation of asthma. All children requiring a loading dose received the correct 5mg/kg bolus however some children over 12 years of age received higher infusion rates than currently recommended. Serum levels >10mg/l are achieved in only 12% of patients following initial loading, and the majority of children require top up aminophylline doses which may delay treatment response. Of the patients with multiple admissions there is consistency with the serum levels achieved. The timing of serum theophylline measurement following loading is

inconsistent and the precise serum theophylline level 30 minutes after loading is not known in many patients.

Children with serum theophylline levels <10mg/l were found to have a significantly longer length of stay compared with those >10mg/l (7.9 vs 15.9 p=0.039). Based on these findings, a causal link between higher serum levels and worse clinical outcomes cannot be established. It is an aminophylline infusion, rather than loading that achieves therapeutic levels. Sicker children are less likely to have their infusions stopped and therefore achieve levels >10mg/l, whilst children who demonstrate clinical improvement are more likely to have aminophylline therapy terminated, despite having subtherapeutic serum levels.

The findings from literature investigating the aminophylline pharmacokinetics in children following intravenous aminophylline therapy is conflicting. A loading dose of 5.6 mg/kg has been shown to achieve a concentration of 10 mg/l (n=10) [104] and a PK study using a higher loading dose (6 mg/kg) demonstrated similar results (n = 11) [105]. However, a similar study using the same dosage did not replicate these findings and majority of children were still subtherapeutic and required additional boluses [106].

The findings of this audit are consistent with Chapter 2, which found no correlation between serum levels and clinically relevant outcomes. This work reinforces our earlier conclusions that TDM of aminophylline is unlikely to maximize its efficacy. A previous audit investigating the relationship between serum theophylline levels and clinically relevant outcomes in children suffering an acute exacerbation of asthma

also found no association between serum theophylline levels and hospital length of stay [100]. Limitations of this study include small sample size and an inability to assess all potential side effects. The treatment of acute asthma requires several medicines with similar adverse effect profiles. As all included children received a combination of these medicines it is difficult to establish a causal relationship between aminophylline levels and adverse effects.

4.5 Conclusion

Despite adequate dosing (5mg/kg), therapeutic levels of intravenous aminophylline are not achieved. However, the effectiveness of treatment for acute asthma is no worse if aminophylline does not achieve the therapeutic range in the first 12 hours. The small sample of included participants means it is difficult to draw conclusions.

4.6 Summary

Previous chapters have demonstrated that neither theophylline levels nor dosage predicts aminophylline efficacy. This chapter linked both TDM results and dosages in a prospective analysis. This work found that current recommendations fail to achieve levels 10-20mg/l, but reiterated our findings from Chapter 2 demonstrating that the current therapeutic range does not result in superior asthma outcomes. The pharmacokinetics and clinical response of intravenous aminophylline remains unpredictable. A better understanding of the mechanisms underlying inter individual variation may highlight a subset of patients who benefit most from a particular dose and an important step in developing stratified aminophylline therapy.

Chapter 5: Pharmacogenetics of intravenous aminophylline

5.1 Background

5.1.1 Variability in aminophylline response

The efficacy of antiasthmatic medicines is not equal among all children [69,115,116]. The clinical response to intravenous aminophylline is inconsistent and unpredictable in children suffering an acute exacerbation of asthma, even between patients with apparently identical phenotypes, severities and environmental triggers [67]. Therapeutic drug monitoring represents an effort to tailor aminophylline dosage to the pharmacokinetics of an individual, however Chapter 2 demonstrated that these practices may not maximise benefit of the drug.

There is a poor understanding of the mechanisms underlying interindividual variation in aminophylline metabolism and the relationship between pharmacokinetics, pharmacodynamics and clinical variability remains unclear. If stratified aminophylline therapy is to enter routine clinical practice, there is a need for better understanding of the precise mechanisms underlying these differences.

CYP1A2 is an enzyme that catalyzes the breakdown of theophylline (the active ingredient in aminophylline) into pharmacologically inactive compounds [63] (Chapter 1). Variation of the *CYP1A2* gene may influence aminophylline disposition, which may affect the serum theophylline levels achieved in an individual [117]. A

single nucleotide polymorphism (SNP) is a variation in a single nucleotide occurring in a specific position in the genome, with a population frequency greater than 1% [118]. More than 40 SNPs have been described in *CYP1A2*, the most extensively studied being *CYP1A2*1A* (wild type), **1C*, **1F* and **1J [117]*. The frequency of these variants differs by ethnicity, and the precise allele frequency is not known in Caucasians.

Caffeine is a substrate of CYP1A2, and is commonly used as a probe to conduct in vivo phenotyping [119]. Though the effect of differing *CYP1A2* polymorphisms on the rate of enzyme activity has been demonstrated [120,121], how this translates into clinical effects is not known. A specific investigation into the link between genetics and clinical efficacy is needed to determine whether genotyping *CYP1A2* polymorphisms can act as a potential biomarker for stratified asthma therapy.

5.1.2 Aim

To determine the effect of *CYP1A2* polymorphisms on the clinical outcomes and pharmacokinetics of children with an acute exacerbation of asthma receiving intravenous aminophylline.

5.2 Methods

5.2.1 Study Design

This chapter describes the initial stages a pilot cohort study comparing the outcomes of children receiving aminophylline for an acute exacerbation of asthma based

CYP1A2 polymorphisms. Children with wild type CYP1A2 (*CYP1A2*1A*) were compared to those with other polymorphisms (*CYP1A2*1B*, *CYP1A2*1C* etc). This is an on-going study that will recruit beyond completion of this MPhil.

5.2.2 Study Population

Children who presented to the emergency department with an acute exacerbation of asthma between August 2015 and May 2016 were eligible for this study. Eligible participants were those who attend regular asthma clinics in Alder Hey Children's Hospital. Following recruitment in asthma clinic in April/May 2016, the families of patients were interviewed and permission sought to retrieve hospital records.

A DNA sample was collected from saliva or blood. Saliva samples were the default collection method for DNA using Noragen's Saliva DNA reagent kit. However, if the participant was due to have a finger-prick blood test, venepuncture or blood test taken from a central venous line, as part of routine clinical care we planned to collect DNA via whole blood.

5.2.3 Laboratory analysis

DNA was extracted at the Wolfson Centre for Personalised Medicine, University of Liverpool. A candidate gene approach was used to identify polymorphisms within *CYP1A2.*

The following procedure for isolating DNA from 4mL of preserved saliva samples was followed. Saliva samples were mixed by inversion and 4ml of the sample was

transferred to a centrifuge tube. Proteinase K was added (150 µL), then the sample was then vortexted for 10 seconds and incubated at 55 degrees for 15 minutes. Following incubation, Binding buffer B was added (1.6ml), the sample was vortexed for a further 10 seconds and incubated again at 55 degrees for 15 minutes. Room temperature isopropanol was added (1.6ml) and the sample was mixed by inversion ten times. After the sample was centrifuged for 10 minutes at 4,000 RPM, the supernatant was removed and 70% ethanol was added. The sample was centrifuged for further five minutes, the ethanol removed and the sample rehydrated in TE buffer.

Patients were genotyped for *CYP1A2* polymorphisms using TaqMan relative polymerase chain reaction SNP genotyping assays, with genotyping master mix (Applied Biosistems, Carlsbad, California). Genomic DNA was genotyped using an ABI 7900HT real-time PCR system. All samples were run in duplicate to ensure concordance of the genotype.

5.2.4 Outcomes

The paediatric respiratory assessment measure (PRAM) is used to assess the severity of an acute exacerbation of asthma for the entire paediatric age span [122]. Although PRAM is externally validated, is not routinely used in clinical practice to assess asthma (Table 13). Data was extracted from the hospital meditech™ computer system, however If complete PRAM scores were not available, the maximum PRAM score that could be achieved based on recorded information was

calculated, and divided this by the actual PRAM score measured. We also aimed to compare length of hospital stay, number of days the until the patient was no longer dependent on oxygen therapy, the number of days until the patient required no more than five puffs of inhaled salbutamol every four hours, adverse effects and serum theophylline levels (in mg/l). Case record forms were developed for recording patient data (appendix).

Table 13. The paediatric respiratory assessment measure

	Scoring			
Sign	**0**	**1**	**2**	**3**
Suprasternal retractions	None		Present	
Scalene muscle activity	None		Present	
Air entry	Normal	Decreased at bases	Diffusely decreased	Minimal or absent
Wheezing	None	Expiratory only	Inspiratory and expiratory	Audible without stethoscope or silent chest
Pulse oxygen saturation	95% or higher	92%-94%	<92%	

5.2.5 Environmental Factors

Participants and their families were interviewed to assess exposure to environmental inducers of CYP1A2 enzymes. Smoking status and pack years of patients and cohabitants was assessed. Pharmacy records were retrieved for drugs that are known to induce or inhibit CYP1A2 (Fig 11).

Fig 11. Inducers and inhibitors of CYP1A2 [52]

Enzyme inducing drugs:	**Enzyme inhibiting drugs:**
Insulin	Amiodarone
Methylcholanthrene	Cimetidine
Modafinil	Ciprofloxacin
Nafcillin	Fluoroquinolones
Naphthoflavone	Fluvoxamine
omeprazole	Furafylline
	Interferon
	Methoxsalen
	Mibefradil
	Ticlopidine

5.2.6 Sample Size

To achieve a 90% power difference in the domains of days until discharge, days until on room air and adverse effects, 272, 56 and 58 patients were needed respectively. This calculation has been derived using multiple regression modelling from previously collected audit data and a previous study investigating the effect of *CYP1A2* polymorphisms on theophylline levels [123]. This is pilot work for a larger scale study.

5.2.7 Statistical Analysis

We aimed to perform multivariate analysis and logistic regression modelling to examine the impact of CYP1A2 polymorphisms on the outcomes under investigation. Any statistical difference between genotype ($p<0.05$) would be flagged, and the difference explored.

5.3.8 Ethical Approval

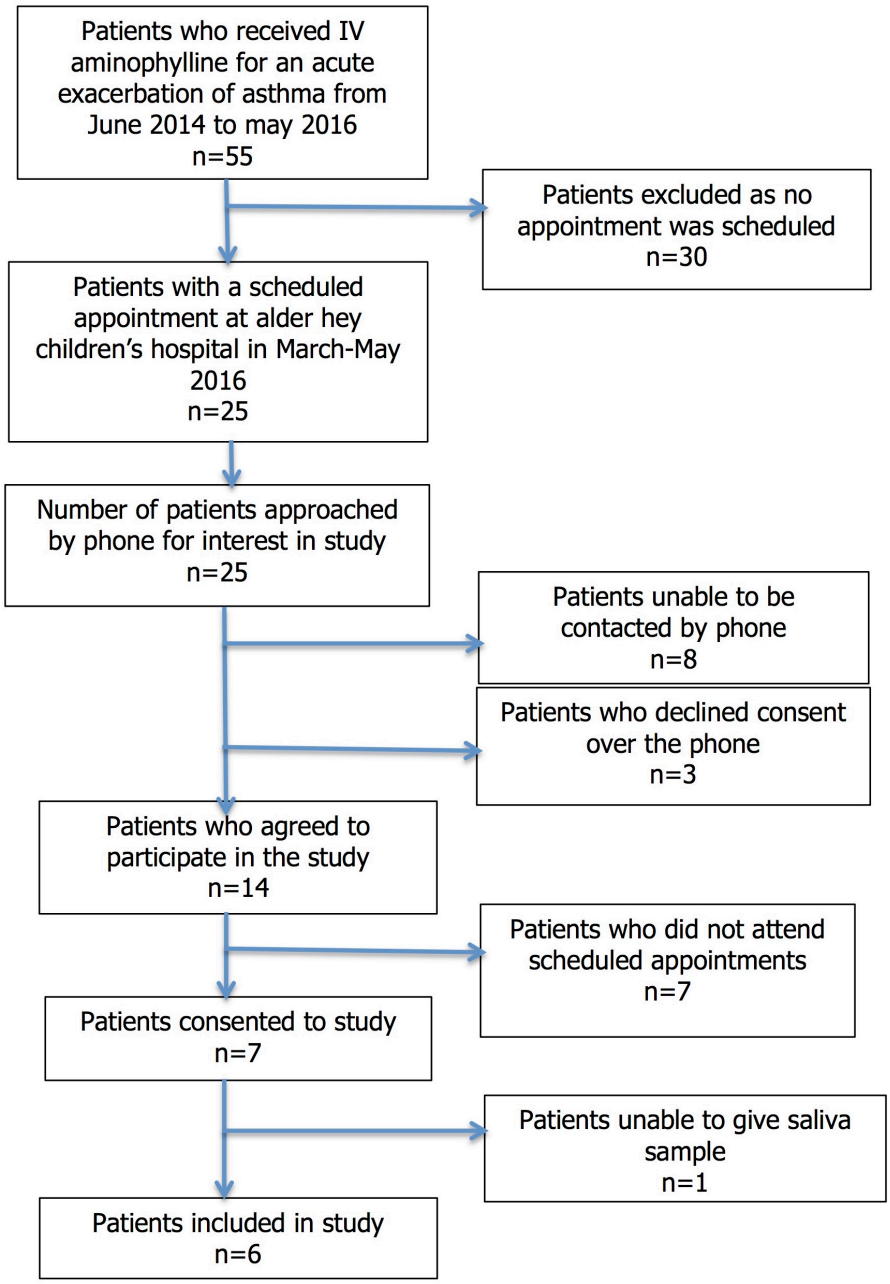
This project is part of the Molecular Genetics of Adverse Drug Reactions in Children (MAGIC) study and has ethical approval. Research Ethics No: 10/H1002/57

5.3 Results

5.3.1 Characteristics of study participants

A total of seven patients were recruited to the study. A DNA sample was unable to be collected in one patient, meaning six patients were included in this study (Fig 12).

Fig 12. Included participants in the cohort study



This study included three girls and three boys, with an average age of 11.3±3.0 years. Three patients were of White British ethnic origin, one patient of mixed White British and Black African origin, one patient of Algerian origin and one patient of

Pakistani origin. Two patients were exposed to environmental smoke and no patients were prescribed enzyme inducing medicines (Table 14).

Table 14. Characteristics of study participants in the cohort study

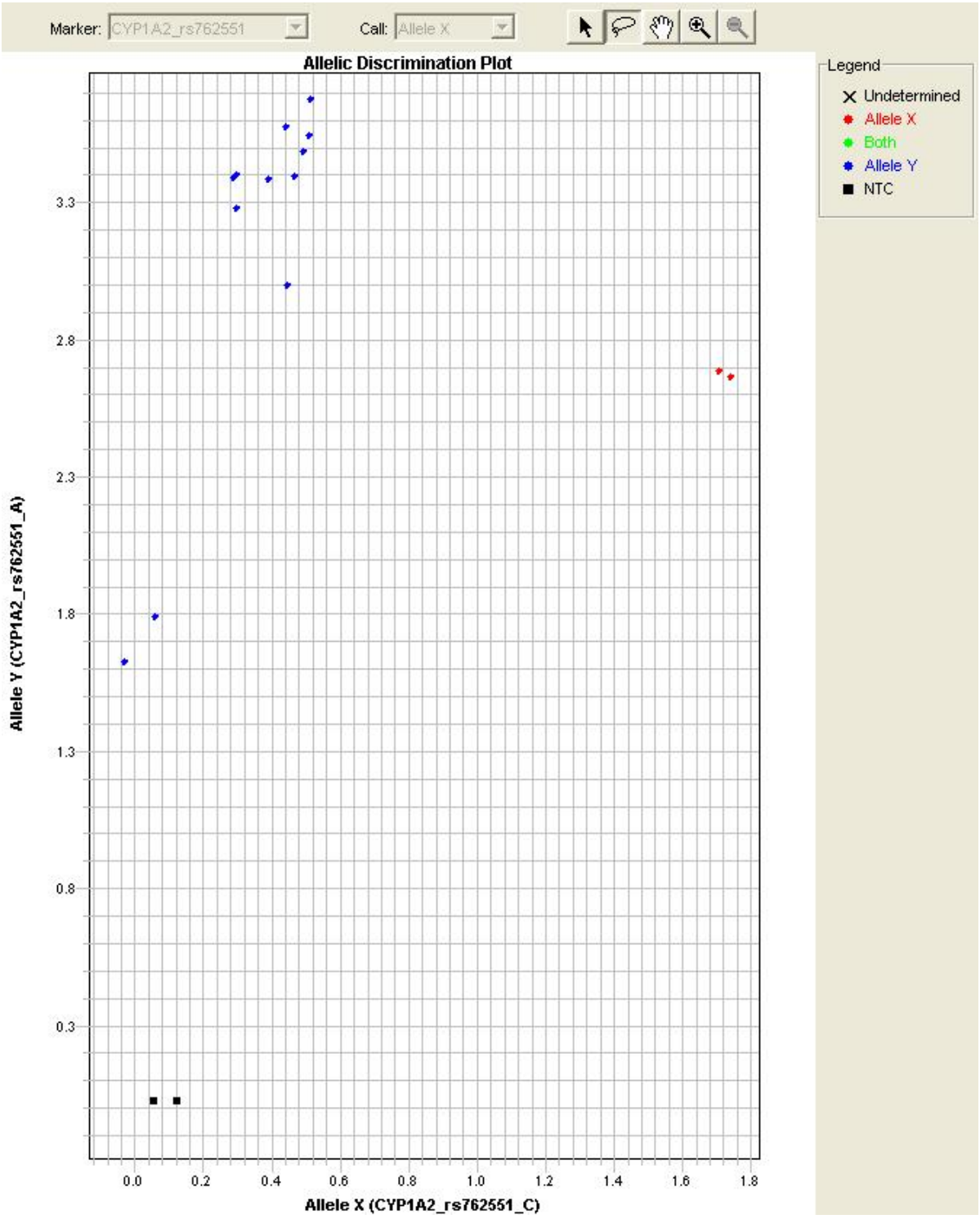
ID	CYP1A2 Polymorphism	Age	Sex	Weight (kg)	Ethnicity	Oral theophylline	Exposure to cigarette smoke
A	CYP1A2*1A	15	F	33.0	White British	Yes	No
B	CYP1A2*1A	10	F	25.2	Algerian	No	No
C	CYP1A2*1A	9	M	27.5	Pakistani	No	No
D	CYP1A2*1A	15	F	80.1	White British	Yes	Yes
E	CYP1A2*1A	11	M	33.8	White British	No	Yes
F	CYP1A2*1F	8	M	28.5	Mixed	Yes	No

Blue: wild type cohort, Red: non wild type cohort

5.3.2 Genotyping

A normal allelic discrimination plot was generated for SNP genotyping (fig 3). Allele X was the *CYP1A2*1A* polymorphism, whilst allele Y was any other *CYP1A2* polymorphism. The blue plots in the upper right hand corner represent the five patients with the *CYP1A2*1A* polymorphism whilst the red plots represent the one patient did not have a wild type polymorphism (Fig 13). Further analysis found this patient to have the *CYP1A2*1F* polymorphism. Each patient is represented by two plots, as all samples were run in duplicate.

Fig 13. Allelic Discrimination plot



Allele X CYP1A2 Polymorphism, Allele Y other, NTC no template control

5.3.3 Outcomes

PRAM score and clinical improvement

Insufficient data was recorded for complete calculations of PRAM scores. Initial assessment prior to aminophylline therapy was more detailed than subsequent assessment meaning comparison before and after treatment could not be made. The average pram score of patients with the wild type polymorphism was 77.4±22% whilst the PRAM score of the patient with *CYP1A2*1F* polymorphism was 67%. Poor subsequent recording of improvement means PRAM scores following aminophylline treatment were unable to be calculated.

Length of stay

The average length of stay in patients with the wild type polymorphism was 5.2±1.5 days, the one patient with the *CYP1A2*1F* polymorphism had a length of stay of three days.

Days until salbutamol five puffs four hourly and days until in room air

These outcomes were not recorded on the hospital computer systems

Adverse effects

Adverse effects were reported in one patient with wild type CYP1A2. This patient experienced vomiting and abdominal pain and required an ondeansetron prescription for nausea. The patient with *CYP1A2*1F* had no documented adverse effects.

Days until in room air and days till salbutamol five puffs four hourly are poorly documented. Clinical outcomes are shown in Table 15.

Table 15. Clinical outcomes of children included in the cohort study

Admission	Initial PRAM	Max PRAM	% PRAM score	Clinical improvement in first 12 hours	Length of stay (days)	Adverse effects
A.1	NR	NR	NR	Yes	4	Hypokalaemia
B.1	6	6	100%	Yes	5	Nausea, abdominal pain
C.1	2	4	50%	No	7	NR
D.1	4	6	67%	Yes	4	NR
D.2	6	6	100%	Yes	7	Nausea
E.1	7	10	70%	Yes	4	NR
F.1	4	6	67%	Unclear	3	NR

NR None reported
Blue: wild type cohort, Red: non wild type cohort

Serum theophylline levels

The results of serum theophylline levels are shown in Table 16

Table 16. Serum theophylline levels achieved of included participants in the cohort study

Admission	Admission theophylline level (mg/l)	mg/kg	Serum level post loading	Serum theophylline level at 12 hours
A.1	<1	4.8	8.9	12.3
B.1	0	5	OC	10
C.1	0	5.1	11.4	17.9
D.1	OC	0.5	15.3	13.8
D.2	<2.0	1.8	8.7	13.2
E.1	0	5.5	8.9	18.1
F.1	<1	4.7	OC	11

OC order cancelled

Blue: wild type cohort, Red, non wild type cohort

All patients with wild type polymorphisms received loading doses or top up loading doses. These ranged from 0.5mg/kg to 5.1mg/kg, the average post loading serum concentration was 10.6±2.9mg/l and the average maintenance theophylline concentration was 14.2±3.2mg/l. The patient with *CYP1A2*1F* polymorphism received a 5mg/kg loading dose, however the serum theophylline level post loading was not reported. This patient achieved a serum theophylline concentration of 11.0mg/l at 12 hours. This patient was not exposed to any known environmental inducers.

5.4 Discussion

This is an on going study and has not yet recruited sufficient participants to assess the effect of *CYP1A2* polymorphisms on the clinical effects, or pharmacokinetics of intravenous aminophylline in children. When further participants are recruited, the indirect effects of environmental inducers such as smoking on clinical outcomes will be evaluated.

Demonstrating a relationship between genome and clinical efficacy is a crucial stage in developing pharmacogenomic information that can benefit patients. If an association between *CYP1A2* polymorphisms and asthma outcomes is found, this would support the use genotyping in stratifying aminophylline therapy in children. This would be used as a companion diagnostic to identify of a subset of patients who benefit most from intravenous aminophylline. The ultimate goal of this process is predictive, pre-emptive personalized asthma care.

The effects of differing *CYP1A2* polymorphisms on theophylline metabolism are poorly understood. Studies investigating this relationship are inconsistent, with some studies demonstrating an effect of the *1F/*1F polymorphism on expression and higher inducibility of CYP1A2 [123,124], whilst another study shows conflicting results [125]. This inconsistency may be due to hidden biases and study design limitations resulting in inconclusive findings. These studies use theophylline as a probe to measure CYP1A2 activity, but do not address how these differences translate into variable treatment response.

Case study evidence shows the effect of *CYP1A2* polymorphisms on the side effect profile of patients taking clozapine [126], and this is the first study aiming to assess how *CYP1A2* polymorphisms may alter the clinical efficacy of intravenous aminophylline in children. This current work represents a pilot study, and is not yet sufficiently powered to have clinically relevant conclusions.

This study is limited by its retrospective use of PRAM scores, as many important measurements such as scalene muscle activity are not recorded on patients notes, meaning most patient scores are incomplete. Future studies investigating the effect of genes on patient response to medicines will need to be prospective, to allow prior determination of clinically relevant outcomes, and rigorous surveillance of adverse effects. Furthermore, this work is unable to account for the all the complex genetic and environmental factors that may play a role in drug response.

Pharmacogenomics must go beyond laboratory measurements if it is to enter the treatment paradigm of asthma. As the concentration-response relationship for intravenous aminophylline is unclear (Chapter 2) future research into aminophylline pharmacogenomics should integrate clinically relevant outcomes with pharmacokinetic data.

5.5 Conclusion

Interindividual variation in aminophylline pharmacokinetics and pharmacodynamics remains poorly understood. This study forms pilot work for a larger scale study and is in its initial stages. It is the first study investigating the link between *CYP1A2* polymorphisms and clinical effects. Further research investigating the genetic determinants of drug response is needed.

5.6 Summary

Previous chapters have demonstrated that serum theophylline levels are poor predictors of asthma outcomes. This chapter aimed to investigate the genetic determinants of aminophylline response of children suffering an asthma exacerbation. An ongoing cohort study has been developed which aims to assess to role of *CYP1A2* polymorphisms on the clinical response of aminophylline. Upon completion, this work may be the initial stages of developing stratified aminophylline treatment algorithms.

Chapter 6: Discussion and Future Work

6.1 Main findings

This work aimed to assess the evidence base for the recommended dosage and monitoring strategies of intravenous aminophylline in children. In this chapter, we will discuss the main implications of our findings and highlight areas for future research.

There is a lack of evidence for the dosage and monitoring strategies of intravenous aminophylline in paediatric asthma management. We found no evidence supporting the recommended therapeutic range of 10-20mg/l and a poor correlation between dosage and efficacy. There is no clear strategy of stratifying aminophylline dosage based on age, weight or serum theophylline levels that maximises its efficacy in acute asthma. Despite good adherence to prescribing guidelines, most children do not achieve serum theophylline levels over 10mg/l. However, our small retrospective study demonstrated that the effectiveness of treatment for acute asthma is no worse if the therapeutic range is not achieved within the first 12 hours. We also found that children with serum theophylline levels over 10mg/l have a significantly longer length of stay in hospital compared with children who are 'subtherapeutic'. Our pilot pharmacogenomic has not yet recruited sufficient participants to assess the association between different *CYP1A2* polymorphisms and aminophylline clearance in children. A summary of thesis findings is shown in Table 17.

Table 17. Summary of thesis findings

Ch.	Aim	Method	Findings
2	Review the evidence base for the therapeutic range 10-20mg/l	Systematic review	There is no evidence regarding the optimum target range of 10-20mg/l in childhood asthma exacerbations
3	Review the evidence for currently recommended dosage guidelines	Systematic review	Current dosing strategies do not maximise the efficacy of intravenous aminophylline
4	Assess how aminophylline is given in clinical practice	Audit	Current dosing strategies do not achieve therapeutic theophylline levels, children within the therapeutic range do not have superior clinical outcomes
5	Assess the association between CYP1A2 and aminophylline efficacy	Cohort study	Study in preliminary stage, effect of CYP1A2 unable to be assessed

6.2 Improving Therapeutic Drug Monitoring Practice

Optimum implementation of TDM requires an understanding of pharmacokinetics. Simply relating a drug concentration to a predefined therapeutic range is not adequate interpretation, and is unlikely to maximize the benefit of intravenous aminophylline [88]. The integration of serum drug concentrations into clinical decisions requires the prior demonstration of a concentration-response relationship. If a clinically relevant target range is established, pharmacokinetic studies are needed to investigate how to achieve target levels through dosing. Understanding the variability in drug clearance rates will help develop dosing strategies that are tailored to meet the needs of individual patients. This work has found a lack of understanding in each of these domains, which is a major barrier to maximizing TDM of IV aminophylline.

TDM is a medical intervention with risks and benefits, and its use in clinical practice requires clear evidence of patient improvement. Inappropriate use of TDM results in

unnecessary painful blood tests, an over reliance on laboratory measurements and laboratory costs. This work has highlighted a lack of understanding of aminophylline pharmacokinetics, meaning the relevance of a serum theophylline concentration in the context of an acute exacerbation of asthma is unclear. This leads to a clinical dilemma, as children can appear to improve despite sub therapeutic concentrations, or experience side effects despite serum levels being within the therapeutic range (Chapter 2). Knowledge of how to maximize efficacy though dosing is lacking (Chapter 3) and currently recommended doses fail to achieve therapeutic levels (Chapter 4). In light of these findings, it is not known whether children benefit from aminophylline TDM versus clinical assessment alone. No randomized controlled trial has compared asthma outcomes of children who receive TDM versus clinical assessment alone, and systematic review data has shown a lack of efficacy of TDM improving patient related outcomes [127].

Though the effect of TDM on patient response to aminophylline is unclear, it may have other clinically relevant applications relevant for the 21st century. TDM technology can be used as a phenotyping procedure to identify slow and fast metabolizers, [128] or to investigate non-response to asthma therapy.

6.3 Developing evidence based therapeutic ranges

For TDM to have relevant application in clinical practice, the upper and lower boundaries of the therapeutic range should be determined by the extent of harm and benefit respectively. Chapter 2 was unable to provide a clear target range for

aminophylline that maximises efficacy and safety. The lack of primary studies investigating the optimum therapeutic range of aminophylline and a poor understanding of its pharmacokinetics in children are further hindrances to developing evidence based therapeutic ranges. A specific investigation into the optimum serum concentrations of aminophylline is required.

A systematic review is the most robust method for evaluating the existing literature around the upper and lower limits of the therapeutic range for a particular drug. Whilst systematic review methods are well established for studies of efficacy or harm, there is no consensus on the optimum methodology for determining therapeutic range for a particular drug. Systematic reviews of TDM practice are an emerging and uncertain field [129-136], but have the potential to be highly relevant with the advent of stratified medicine and individualised treatment. There are significant methodological variations as well as inconsistences in the reporting of existing published systematic reviews of TDM, and there is clearly a need to improve or standardize methods. A peer-reviewed protocol for conducting systematic reviews of therapeutic ranges has the potential to benefit patients receiving drugs that require therapeutic drug monitoring.

The findings in Chapter 2 are not generalizable to the therapeutic range of oral theophyllines for chronic asthma. As relevant outcomes differ between indications, a separate investigation would provide further information on the TDM practices in long term asthma care.

As the evidence base for many therapeutic ranges is poor (Table 18), developing a systematic review protocol has the potential to improve monitoring strategies for a wide range of drugs for several indications.

Table 18. Issues with the current evidence base surrounding therapeutic ranges.

Drug	Indications	Range BNFc	Evidence Base
Phenytoin	Seizure treatment and prophylaxis	10-20mg/l	Improvements of EEG at levels >10mg/l Buchthal 1960 and appearance of nystagmus at 20mg/l (n=12)
Carbamazepine	Seizure treatment and prophylaxis, neuropathic pain, psychiatric indications	4–12 mg/l	Based on seizure control of adults over 21 days n=45 Cereghino 1974
Gentamicin	Gram negative bacterial infections	5–10 mg/l	Arbitrary therapeutic range Begg 1999
Teicoplanin	Antibiotic against gram positive bacteria	15-60mg/l	Arbitrary therapeutic range Begg 1999
Lithium	Treatment and prophylaxis of mania, bipolar disorder, recurrent depression, aggressive or self-harming behaviour	0.4–1 mmol/l	Based on the treatment of acute mania after 7-10 days of treatment n=68 Stokes 1976 A review of 5 studies recommends lower levels Severus 2008
Digoxin	Atrial fibrillation Heart failure	0.8 to 2.0 ng/ml*	Upper limit based on only 4 types of adverse effect n=131 Smith 1970
Theophylline	Reversible airways disease	10-20mg/l	Based on an improvement of spirometry from participants not suffering an acute exacerbation

Indirect evidence is was an important resource in gaining further insight into the practical applications of TDM and dosage in Chapters 2 and 3. Indirect evidence may provide important answers to clinical questions, and guide future research goals in areas where there is a lack of primary research such as paediatric pharmacology. To maximize benefit from indirect evidence there is a need to improve reporting in primary studies. This includes better reporting of TDM results achieved, the use of laboratory techniques for determining serum concentrations, using an *a priori* technique for assessing adverse effects and the development of a risk of bias tool for use in systematic reviews of therapeutic ranges.

6.4 Stratifying dosage: Beyond one size fits all

Aminophylline is prescribed to a wide age range of children at different stages of development, which may affect its pharmacokinetics and pharmacodynamics. Standardized dosing recommendations cannot account for the variability in clinical features or severities of acute asthma. Traditional pharmacokinetic studies fail to account for the heterogeneity of the paediatric population [102,104-106]. These models assume a linear relationship between weight and dose and cannot adjust for the rapid changes in rates of organ maturation, blood flow, or body composition that take place in childhood. Developing stratified dosing will require pharmacological research that is able to account for interindividual variation across a population.

Physiologically based pharmacokinetic modeling (PBPK) can be used to improve understanding of drug disposition in children. Computer models can be used to map

the complex drug transport scheme onto a physiologically realistic compartmental structure. This mathematical model can be used to predict the absorption, distribution, metabolism and excretion of aminophylline, and can incorporate anatomical and physiological age related changes that take place in childhood. These include differing tissue compositions, relative organ weights, blood flow rates and the maturation processes of renal and enzymatic function [137,138]. This circumvents the ethical issue of recruiting human participants to pharmacokinetic studies. PBPK models can also incorporate variability and uncertainty within a population, which is necessary when investigating interindividual variation [139].

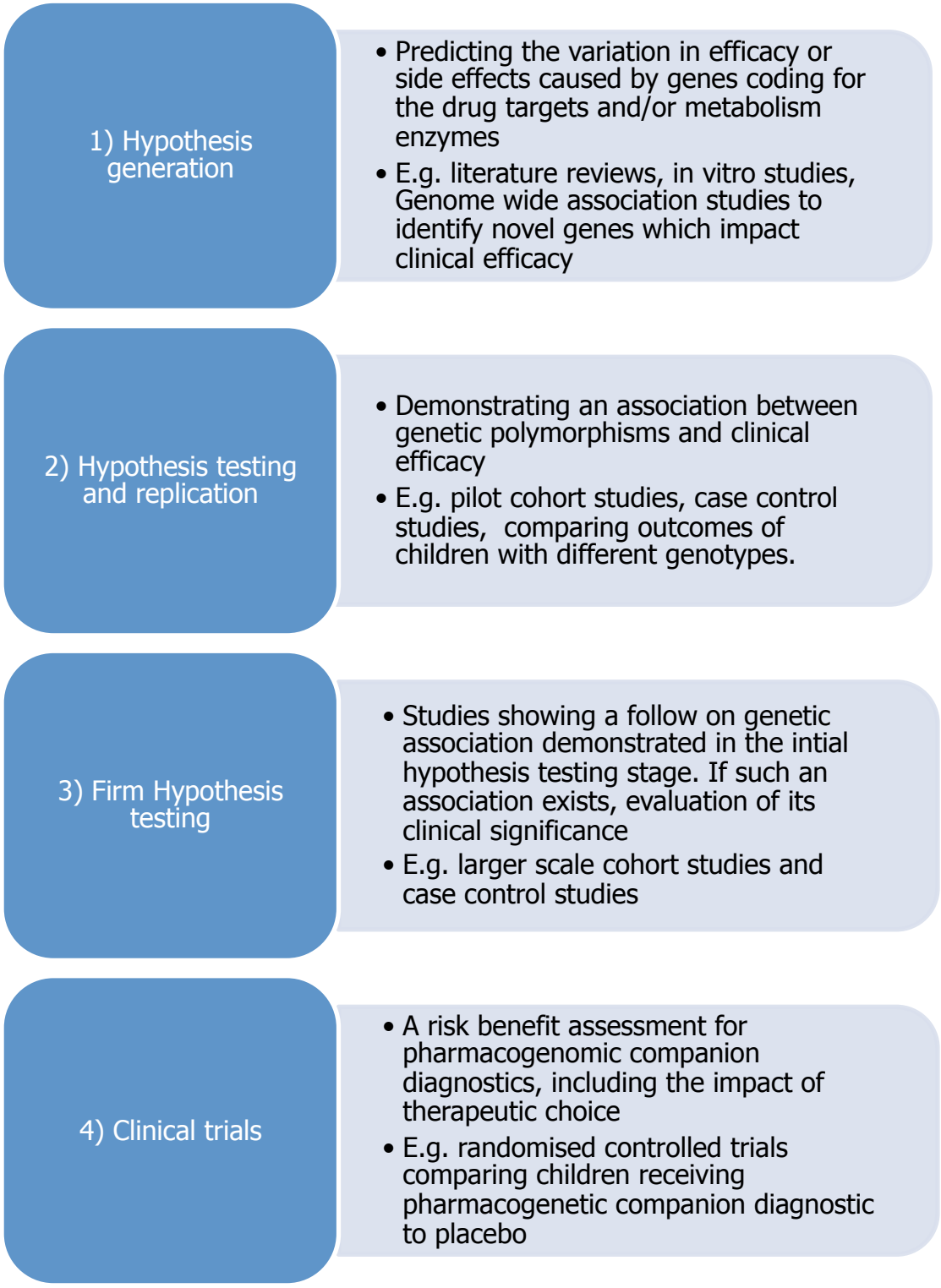
PBPK has limited usage in pharmacological research. The inherent complexity and unknown phenomenon involved in pharmacokinetics mean PBPK modeling is vulnerable to a large degree of oversimplification and the reliability of models to predict serum concentrations after the administration of a drug is still unclear [140]. There is growing confidence in PBPK as models become more sophisticated and it is likely that the results of PBPK will be able to improve paediatric dosing in clinical practice. This work contributes foundations for the use of PBPK modeling in children receiving intravenous aminophylline [141].

6.5 Aminophylline pharmacogenomics: from bench to bedside

A stepwise approach to developing treatment algorithms based on genetic information has been proposed (Fig 14), this is a complex multi stage process involving various study designs and different levels of evidence [142]. Pharmacogenomics has not yet entered routine asthma treatment. This work has highlighted practical and methodical challenges in translating hypotheses of genetic

association into real life dosing and monitoring adjustments. These include difficulty in generating adequately powered studies due to the small pool of eligible participants, and challenges in measuring clinically relevant outcomes when relying on historical patient records.

Fig 14. Stages of developing clinically applicable pharmacogenomics. [142].



Genes encoding for drug metabolism enzymes are the most widely studied candidate genes for pharmacogenomics. This is based on the principle that modulation of

pharmacokinetics alters drug concentrations in the body, which determines both its therapeutic efficacy and adverse effects [143]. If genotyping of drug metabolism enzymes is to enter clinical practice, there must be an established relationship between serum concentrations and clinical response. Chapter 2 demonstrated that currently accepted therapeutic ranges have a poor evidence base, and do not always translate into clinical benefit, or prevention of adverse effects. This is a major barrier to overcome if genotyping drug metabolism enzymes are developed as companion diagnostics in stratifying aminophylline dosing.

There is a need to increase the numbers of participants involved in in the preliminary stages of pharmacogenomic research if its findings are to benefit patients. Many studies are underpowered because of the low allele frequency of many polymorphisms, and identifying relevant cohorts is difficult, as genotyping is not part of standard clinical care. Recruitment problems are amplified in paediatrics, where there is a smaller pool of eligible participants and a complex consent process [144].

Better understanding of the link between genes and aminophylline variability requires an appreciation of the high number of chromosomal regions being associated with drug response. There is evidence that variability in the *CYP1A2* gene affects this disposition of several substrates, but this relationship alone cannot provide a comprehensive explanation for the genetic determinants of drug response. Interindividual variation is unlikely to be coordinated by a single protein, and there is a need to develop pharmacogenomic research beyond drug metabolism enzymes. Better understanding of the role of drug transporters, receptors and transduction

pathways will provide a more complete picture of the mechanisms underlying asthma variability. There is a large number of potential genes that may affect drug response, including genes which affect hepatic/renal elimination and genes which influence the transport of aminophylline into specific cells. The association between these factors and patient response to aminophylline response has not yet been investigated.

Findings from studies investigating the role *CYP1A2* in developing pharmacogenomics are inconsistent [120,121,123-125,145-148]. Lack of reproducibility of results from observational studies is a key barrier to understanding and confirming the therapeutic relevance of candidate genes. As pharmacogenomics is a relatively new discipline there is a need to develop adequate study designs that account for the complexity of drug response.

Genome wide association studies (GWAS) may be an important study design in generating hypotheses that can be tested and then subsequently translated into clinical trials. These seek to identify variations that modify the response to a certain drug throughout the entire genome, rather than a single candidate gene. They may be useful in investigating pharmacodynamic variability, where the profile of potential SNPs influencing drug response is vast. There are distinct advantages and disadvantages of this method when compared to candidate gene analyses (Table 19), and GWAS may be a vital tool in expanding our knowledge of the unknown genetic influences on drug response.

Table 19. Candidate gene analysis vs genome wide association studies

	Candidate gene study	**Genome wide association study**
Selection of genes	SNPs selected by the researcher	Whole genome
Number of genes selected	Up to 10 SNPs	Millions of SNPs
Use in pharmacogenomic development	Hypothesis testing	Hypothesis forming
Cost	Lower	Higher

6.6 Clinical Trials and Stratified Medicine

Current randomised controlled trials (and thus, systematic reviews) comparing aminophylline to placebo lack important analyses that are relevant to stratifying asthma therapy. Firstly, the uncertainty surrounding the optimum dosage and monitoring strategies is an important confounding factor, and many meta-analyses include studies with widely differing administered doses as shown in Chapter 3. Secondly, there have been no RCTs that include an investigation of genetic differences related to outcomes. As asthma outcomes are analysed according to assigned treatment arms, it is likely that study groups were composed of good and bad responders. Due to the small pool of eligible study participants in paediatric asthma research, it is likely these studies lacked sufficient power related to

responsiveness. Appreciation of variability will require large-scale studies that can account for the interindividual variation in treatment response.

Only when the potential of intravenous aminophylline is maximised, can it be definitively compared to placebo or other treatment in clinical trials. Uncertainty regarding its dosage and monitoring means the place of aminophylline therapy in acute asthma remains unclear. This will allow evaluation of whether aminophylline is a superior treatment to intravenous salbutamol or magnesium sulphate. This thesis provides important groundwork for clinical trials that adequately represent the optimum risk benefit ratio of intravenous aminophylline in the treatment of an acute exacerbation of asthma.

6.7 Final Conclusion

Prescribing practices of aminophylline in paediatric acute asthma have a very limited scientific rationale. There are major gaps in knowledge in how to maximise aminophylline efficacy through therapeutic drug monitoring. Pharmacokinetic studies of aminophylline in children are scarce and improving understanding requires deriving the maximum content from the limited data in paediatric studies. Stratifying asthma therapy is complex and will require research into systematic review methodologies and large-scale pharmacogenomic studies. This work provides the initial steps towards large-scale studies aiming to assess aminophylline efficacy and variability.

7 References

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8 Appendix

Appendix 1 Excluded Studies

Table 1. Chapter 2, Full text articles excluded with reasons

Study	**Reason**
Singhi 2014 [1]	Did not measure theophylline levels
Zainudin 1994 [2]	Includes adults and children, children not treated separately in results and statistical analysis
Ibrahim 1993 [3]	Did not measure theophylline levels
Shilalukey 1993 [4]	Did not measure any of the stated primary outcomes
Bowler 1987 [5]	Adult study
Carrier 1985 [6]	Adult study
Katz 1981 [7]	Includes adults and children, children not treated separately in results and statistical analysis
Blumenthal 1979 [8]	Correspondence article
Josephson 1979 [9]	Includes adults and children, children not treated separately in results and statistical analysis
Hambleton 1979 [10]	Did not measure theophylline levels

Table 2. Chapter 3, Full text articles excluded with reasons

Ref.	Reason
Tiwari 2014 [11]	No other studies used ketamine as a comparator drug. Unable to compare across studies
Nagao 2007 [12]	Supplement article, no full text available
Alcaraz 2007 [13]	Not a randomised controlled trial
Yamauchi 2005 [14]	Adult study
Emerman 2001} [15]	Cohort study
Tomac 1996 [16]	Not an RCT
McKenzie 1994 [17]	Editorial article
Zainudin 1994 [2]	Adult study
Janson 1992 [18]	Adult study
Vilsvik 1990 [19]	Adult study
Stine 1989 [20]	Includes adults and children, not treated separately in analysis
Fanta 1986 [21]	Adult study
Seki 1986 [22]	Not an RCT
Siegel 1985 [23]	Supplement article only, full text not available
Rossing 1981 [24]	Adult study
Goldberg 1980 [25]	Not a randomised controlled trial
Rossing 1980 [26]	Adult study
Evans 1980 [27]	Adult study
Josephson 1980 [28]	Adult study
Wolfe 1978 [29]	Adult study
Tribe 1976 [30]	Adult study
Pierson 1971 [31]	Did not report dose
Fanta 1982 [32]	Adult study

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Appendix 2 Pharmacogenomic CRF

UNIVERSITY OF LIVERPOOL

Molecular Genetics of Adverse Drug Reactions in Children (MAGIC)

Pharmacogenomics of Aminophylline

Study Code:

Site Code:

Subject Number:

Patient Recruitment Date:

Patient Initials:

Recruiting Health Professional:

Name:

Hospital/GP Practice:

Work Telephone Number:

Work Email Address:

Chief Investigator:
Prof M. Pirmohamed
The Wolfson Centre for Personalised Medicine,
Department of Pharmacology, University of
1-5 Brownlow Street,Liverpool, L69 3GL

Mr. Lewis Cooney: MPhil Student,
Email: hllcoone@student.liv.ac.uk

Dr Dan Hawcutt, Senior Lecturer Paediatric Pharmacology
Email: d.hawcutt@liv.ac.uk

General enquiries: Naomi.Rogers@alderhey.nhs.uk

General Guidelines for CRF Completion

Please complete the Case Report Form (CRF) as thoroughly as possible and then post or fax a photocopy of the completed CRF to the lead coordinating centre, along with the anonymised discharge summary and/or additional anonymised reports (e.g. skin biopsy reports, CXR, CT scan results etc).

The structure of the CRF is shown in the following diagram;

Even Pages	**Odd Pages**
Contain notes on how to complete the adjacent → odd numbered page	To be completed

All forms should be completed in black ink in a clear manner. Any changes or corrections should be made by drawing a line through the data, entering the corrected information and initialling and dating the change.

Following standard notation should be used in the event that values or answers cannot be provided:

- NA: Not applicable
- NK: Not known
- ND: Not done
- NR: Not retrievable/Not available

Please ensure that when referencing medications and chemicals you detail the GENERIC name and not the brand name

Part A Inclusion/Exclusion criteria – Notes

[1] The patient **must** be given a Patient Information Leaflet and Consent Form to be included in the study. If the patient is <16 consent must be granted by Parent or Guardian/Nominated Parent or Guardian, else if >16 patient must give consent.

[2] If the patient is participating in another study, it is essential to discuss eligibility to participate with the Principal Investigator prior to ticking "yes" or "no".

Inclusion/Exclusion Criteria

Please tick 'yes' or 'no' to **all** questions

A		Yes	No
1.	Patient/Participant willing to take part in study if >16 years of age at recruitment		
2.	Patients/Participants parent or guardian willing to consent to study if <16 years of age at recruitment		
4.	Assent obtained from competent young person? (assessed on case by case basis) Version [___] Version dated [DD / MM / YYYY] Date given [DD / MM / YYYY]		
5.	Patient information leaflet read by Patient/Parent or Guardian/Nominated Parent or Guardian**[1]** Version [___] Version dated [DD / MM / YYYY] Date given [DD / MM / YYYY]		
6.	Parent information leaflet read by Parent/guardian? Version [___] Version dated [DD / MM / YYYY] Date given [DD / MM / YYYY]		
7.	Written informed consent obtained? **[1]** Version [___] Version dated [DD / MM / YYYY] Date given [DD / MM / YYYY]		
8.	Patient has a diagnosis of asthma		
9.	Patient has attended Alder Hey Children's hospital with an acute exacerbation of asthma requiring treatment with intravenous aminophylline		

Exclusion Criteria

Please tick 'yes' or 'no' to **all** questions

B		Yes	No
9.	Patient/Participant unwilling to take part in study if >16 years of age at recruitment		
10.	Patients/Participants parent or guardian unwilling to consent to study if <16 years of age at recruitment		
11.	Competent older participant unwilling to assent (competence assessed on a case by case basis)		
12.	Unable to nominate a Parent/Guardian		
13.	Patient is, in the opinion of the Investigator, not suitable to participate in the study.		

Patient Eligible for study [2]	Yes ☐ **Patient included in the Please complete CRF**	No ☐ **Patient Not included in the study**

Recruitment Information – Notes

[1] Please enter the patient's date of birth at the time of recruitment.

[2] Ethnic origin as self reported, by the patient or documented in casenotes. Please note that we appreciate it may be difficult to obtain Parents information, so we would be very grateful for any information provided.

Please use codes as listed:

1. White
2. White Irish
3. Other White
4. Mixed: White and Black Caribbean
5. Mixed: White and Black African
6. Mixed: White and Asian
7. Other mixed background
8. Indian
9. Pakistani
10. Bangladeshi
11. Other Asian background
12. Caribbean
13. African
14. Other Black background
15. Chinese
16. Other ethnic group (please specify)
17. Not Known

Recruitment Information

Patient Demographics

Sex	Male ☐	Female ☐	
Date of Birth [1]			
Patient Height		(2 decimal places)	NK ☐
Patient Weight		(2 decimal places)	NK ☐

Ethnic origin [2]

Own	☐	Specify		Country of Birth	
Mother	☐	Specify		Country of Birth	
Father	☐	Specify		Country of Birth	

Previous Medical History - Notes

[1] Has patient ever had any medical or surgical interventions prior to the recruitment visit?

Not Recorded = section not relevant to study arm

Previous Medical History

1.	**Has patient ever had any medical or surgical**	Yes ☐ No ☐ Not Recorded ☐
2.	**Malignancy**	Yes ☐ No ☐ Specify ☐
3.	**Respiratory Disease**	Yes ☐ No ☐ Specify ☐
4.	**Cardiac Disease**	Yes ☐ No ☐ Specify ☐
5.	**Gastrointestinal Disease**	Yes ☐ No ☐ Specify ☐
6.	**Neurological Disease**	Yes ☐ No ☐ Specify ☐
7.	**Haematological** *(not*	Yes ☐ No ☐ Specify ☐
8.	**Immunological**	Yes ☐ No ☐ Specify ☐
9.	**Endocrine**	Yes ☐ No ☐ Specify ☐
10.	**Skin**	Yes ☐ No ☐ Specify ☐
11.	**Eyes**	Yes ☐ No ☐ Specify ☐
12.	**Ears**	Yes ☐ No ☐ Specify ☐
13.	**Musculoskeletal**	Yes ☐ No ☐ Specify ☐
14.	**Renal**	Yes ☐ No ☐ Specify ☐
15.	**Psychiatric**	Yes ☐ No ☐ Specify ☐
16.	**Other Disease**	Yes ☐ No ☐ Specify ☐ Specify ☐ Specify ☐ Specify ☐ Specify ☐

Blood Sample / Saliva Sample Collection - Notes

[1] You will be asked to collect **either** a blood or saliva sample by the lead co-ordinating centre.

The quality of the DNA from a blood sample is much higher than from saliva, so we would be grateful if you could collect a blood sample from the patient were possible.

Blood sample / Saliva Sample Collection [1]

Blood sample collected for DNA? ***(Purple top EDTA sample, if possible please collect 5-9ml. Minimum requirement is 2ml)***	Yes ☐ Date & time collected: DD/MM/YYYY – HH:MM Amount collected: No ☐ Reason not collected: N/A ☐
Saliva sample collected for ***(2mls self collection kit)***	Yes ☐ Date & time: DD/MM/YYYY – No ☐ Reason not: N/A ☐

(Part B)Regular medications/chemicals

[1] Please detail any regular medications including preventer inhalers, reliever inhalers, topical steroids, nasal steroids and leukotriene receptor agonists

(Please specify the generic name of the Medication/Chemical and <u>NOT</u> the brand name)

(Part B) List of Medications/Chemicals

	Medication		Dose			
	Formulation		Route **[3]**		Frequency	
	Start date	DD/MM/YYYY	Stop date	DD/MM/YYYY		
	Medication		Dose			
	Formulation		Route **[3]**		Frequency	
	Start date	DD/MM/YYYY	Stop date	DD/MM/YYYY		
	Medication		Dose			
	Formulation		Route **[3]**		Frequency	
	Start date	DD/MM/YYYY	Stop date	DD/MM/YYYY		
	Medication		Dose			
	Formulation		Route **[3]**		Frequency	
	Start date	DD/MM/YYYY	Stop date	DD/MM/YYYY		
	Medication		Dose			
	Formulation		Route **[3]**		Frequency	
	Start date	DD/MM/YYYY	Stop date	DD/MM/YYYY		
	Medication		Dose			
	Formulation		Route **[3]**		Frequency	
	Start date	DD/MM/YYYY	Stop date	DD/MM/YYYY		
	Medication		Dose			
	Formulation		Route **[3]**		Frequency	
	Start date	DD/MM/YYYY	Stop date	DD/MM/YYYY		
	Medication		Dose			
	Formulation		Route **[3]**		Frequency	
	Start date	DD/MM/YYYY	Stop date	DD/MM/YYYY		
	Medication		Dose			
	Formulation		Route **[3]**		Frequency	
	Start date	DD/MM/YYYY	Stop date	DD/MM/YYYY		

Chronic Asthma History - Notes

[1] Examples of triggers include animal dander, exercise, stress, pollen, certain drugs
Answer yes if a serum IgE level has been recorded on the alder hey meditech™ system

[2] Refers to metered dose inhalers (MDIs) which give the medicine in a spray form (aerosol). Reliever examples include Ventolin, Airomir and Salamol, preventer examples include beclometasone dipropionate, budesonide, fluticasone propionate and mometasone furoate

[3] Refers to NHS immunization schedule which applied at the time of birth. A full immunization status includes

- 5-in-1 (DTaP/IPV/Hib)
- Pneumococcal (PCV)
- Rotavirus if born before September 2013
- Meningitis B if born before September 2015
- Meningitis C
- Measles Mumps and Rubella (MMR)

Chronic Asthma History

Symptoms	Age at onset of symptoms ☐
	Known triggers **[1]** Yes ☐ No ☐
	If yes please tick all that apply
	Animal fur ☐ Pollen/grass ☐
	Dietary triggers ☐ Exercise ☐
	Cold air ☐ Emotion/stress ☐
	Medicines ☐ Cigarette smoke ☐
	Other ☐
Does the patient have any history of atopic disease?	Nocturnal cough Yes ☐ No ☐
	Diagnosis of eczema at any time Yes ☐ No ☐
	If YES, current eczema Yes ☐ No ☐
	Hayfever Yes ☐ No ☐
	Other allergies Yes ☐ No ☐
	If YES please specify ☐
	Have IgE levels been measured? **[2]** Yes ☐ No ☐
	If YES:
	Most recent level ☐ Date DD/MM/YY
	Highest level ☐ Date DD/MM/YY
Asthma maintenance	On average, how often is a reliever inhaler used?
	Monthly ☐ Daily ☐
	Weekly ☐ Twice Daily ☐
	Every other day ☐ More than twice daily ☐
Spacer device usage	When taking a RELIEVER inhaler, how often is a spacer used?
	Always ☐ Sometimes ☐ Rarely ☐ Never ☐
	When taking a PREVENTER inhaler, how often is a spacer used?
	Always ☐ Sometimes ☐ Rarely ☐ Never ☐
	Number of courses of oral steroids since August 1st 2015 ☐
Immunizations [3]	Immunisation status Full ☐ Partial ☐ None ☐
	Missed immunisations ☐
Treatment history	Has the patient EVER experienced an asthma attack requiring:
	IV salbutamol ☐ HDU admission ☐
	ITU admission ☐ Intubation ☐

Birth History

BIRTH HISTORY

Obstetric history	
Gestational age at birth	☐ Weeks ☐ Days
Birth weight	☐
Was NICU admission required?	Yes ☐ No ☐
Was Intubation required?	Yes ☐ No ☐
Was Ventilation required?	Yes ☐ No ☐
Home oxygen required?	Yes ☐ No ☐
Was this a singleton pregnancy?	Yes ☐ No ☐ If no please state otherwise Twin/Triplet/Other (.....)

Social History - Notes

[1] Answer **yes** if the patient shares an address with anyone who smokes at least one cigarette a day, whether inside or outside the house

[2] Detailed the combined number of cigarettes smoked by all the smokers with whom an address is shared, if the patient lives with only one smoker, this figure will be the number of cigarettes smoked by that person.

[3] An electronic cigarette is any device containing a nicotine-based liquid that is vaporized and inhaled

[4] Tick yes if the patient shares a house with any domesticated animals including dogs, cats, budgerigars, hamsters, gerbils, guinea pigs, ferrets etc

[5] Caffeinated drinks include tea, coffee, Coca-Cola, energy drinks

Social History

1. Smoking history of patients	Does the patient live with a smoker? **[1]**	Yes ☐	no ☐
	If YES, How many smokers does the patient live with	☐	
	Total number of cigarettes smoked in the house a day **[2]**	☐	
	Does the patient live with an electronic cigarette user? **[3]**	Yes ☐	No ☐
2. Smoking history of patient	Does the patient smoke?	Yes ☐	No ☐
	If YES how many cigarettes a day are smoked?	☐	
	Does the patient use an electronic cigarette?	Yes ☐	No ☐
3. Pets	Does a patient live in a house with animals [4]	Yes ☐	No ☐
	If YES Please detail	☐	
4. Caffeine intake	Does that patient drink caffeinated drinks? [5]	Yes ☐	No ☐

Short Synacthen Test - Notes

Please detail the **most recent** short synacthen test

[1] Adrenal insufficiency is excluded by an incremental rise in cortisol of > 200 nmol/L and a 30 min value > 600 nmol/L.

Short Synacthen Test

Short Synacthen Test	DD/MM/YY
Date	DD/MM/YY
Initial Cortisol level	nmol/L
Dose of Synacthen Given	micrograms
Post synacthen Cortisol level	
Adrenal insufficiency [1]	Yes No

Acute Asthma History – Serum Levels

[1] This form to complete details of the first acute exacerbation requiring IV aminophylline which occurred after 16th August 2015. If more than one exacerbation has occurred, please use the forms on appendix 1 provided to complete the 2nd, 3rd 4th exacerbation etc, and any subsequent admissions (second, third, fourth etc) in appendix 1.

[2] Oral theophylline includes the following preparations: Uniphyllin Continus®, Nuelin SA® 250, Nuelin SA® 175, Slo-Phyllin®, Slo-Phyllin®

[3] ONLY answer this section of the patient takes one of the above medications. Leave this section blank if none of these prescribed

[4] ONLY answer if the patient DOES NOT take one of the above medications. Skip to maintenance dose section if this is not the case

Acute Asthma History – Serum Levels

1	**Patients on home theophylline**	Date of admission ____ Date of discharge DD/MM/YY Was the patient taking oral theophylline on admission? Yes ☐ No ☐ If yes, skip part 3
2	**Loading dose**	What loading dose IV aminophylline was given? ____ mg Time started HH:MM Serum concentration on completion of the loading ____ mg/l Time HH:MM Serum concentration on admission ____ mg/l Time HH:MM If patient was taking home theophylline please skip to part 4
3	**Patients not on home theophylline**	Was a top up loading dose required? Yes ☐ No ☐ If Yes Dose given ____ mg Time started HH:MM Serum concentration post top up ____ mg/l Time HH:MM
4	**Maintenance dose**	Infusion rate of first infusion ____ ml/hr Subsequent theophylline level ____ mg/l Time HH:MM

Acute Asthma History: Clinical Data – Notes

[1] The paediatric respiratory assessment measure (PRAM) score is as follows

	Scoring			
Sign	**0**	**1**	**2**	**3**
Suprasternal retractions	None		Present	
Scalene muscle activity	None		Present	
Air entry	Normal	Decreased at bases	Diffusely decreased	Minimal or absent
Wheezing	None	Expiratory only	Inspiratory and expiratory	Audible without stethoscope or silent chest
Pulse oxygen saturation	95% or higher	92%-94%	<92%	

Please do not include scaline muscle activity in the assessment, therefore the PRAM score will be out of 10

Acute Asthma History: Clinical Data

Initial assessment

Time HH:MM

PRAM score

To be completed as fully as possible

Supra sternal retractions None ☐ Present ☐ NK ☐

Scalene muscle activity None ☐ Present ☐ NK ☐

Air entry recorded Yes ☐ No ☐

Normal ☐ Decreased at bases ☐ Diffusely decreased ☐ Absent ☐

Wheezing recorded Yes ☐ No ☐

None ☐ Expiratory only ☐ Expiratory & inspiratory ☐ Without steth ☐

Pulse oximetry recorded Yes ☐ No ☐

>95% ☐ 92%-94% ☐ <92% ☐

Paediatric asthma care pathway notes

First review of treatment Time HH:MM

Please tick ONE box

Improving ☐ Unchanged ☐ Inadequate response ☐ Worsening ☐ Dischar ☐

Second Review of treatment Time HH:MM

Please tick ONE box

Improving ☐ Unchanged ☐ Inadequate response ☐ Worsening ☐ Dischar ☐

Time transferred from A&E to ward HH:MM

Ward Care

Did the patient require any of the following during ENTIRE admission?

	Yes	No	
IV Salbutamol	☐	☐	Number of boluses ☐
IV magnesium	☐	☐	Number of boluses ☐
PICU admission	☐	☐	
Mechanical ventilation	☐	☐	

Date of discharge from PICU if admitted DD/MM/YY

Date patient was in room air DD/MM/YY

Acute Asthma History: Adverse Effects

[1] Other adverse effects include

- Gastrointestinal
  - Diarrhoea
- Neurological
  - Agitation
  - Hallucination
  - Ataxia
  - Insomnia
  - Confusion
- Cardiovascular
  - Asystole
- Metabolic
  - Ketoacidosis
  - Lactic acidosis
  - Hyper glycaemia
- Miscellaneous
  - Rhabdomyolysis
  - Leucocytosis

[2]

Enzyme inducing drugs include:

- Insulin
- Methylcholanthrene
- Modafinil
- Nafcillin
- Naphthoflavone
- omeprazole

Enzyme inhibiting drugs include:

- Amiodarone
- Cimetidine
- Ciprofloxacin
- Fluoroquinolones
- Fluvoxamine
- Furafylline
- Interferon
- Methoxsalen
- Mibefra

Acute Asthma History: Adverse Effects

Adverse effects [1]	Did the patient experience a suspected adverse effect during this admission? Yes ☐ No ☐ If Yes please detail Group 1 Cardiac Arrhythmias ☐ Seizure ☐ Group 2 Nausea ☐ Abdominal pain ☐ Agitation/tremor ☐ Hallucinations ☐ Other ☐ Please detail Serum theophylline level at time of adverse effect if known mg/l
Concomitant medication [2]	Was the patient taking enzyme inducing/inhibiting drugs at the time of this admission Yes ☐ No ☐ Name of drug

Name	Signature	Date
		DD/MMM/YYYY